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[Jour. Indian Chem. Soc., Vol. 30, No. 10, 1953]

CONDENSATION OF KETONES WITH CYANOACETIC ESTERS PART II. EFFECT OF PRIMARY AMINES ON SECONDARY AMINE CATALYSTS AND THE EFFECT OF SOLVENT

By Sukh Dev

Primary amines, like benzylamine, have been found to have a strong "promotor" effect on the catalytic efficiency of secondary amine salts in the condensation of ketones with ethyl cyanoacetate.

A change of the solvent in the condensation of ethyl *cyclo*pentane-1 oxo-2-*β*-propionate (III) with ethyl cyanoacetate has yielded unexpected results.

In Part I of this series (this *Journal*, 1953, **30**, 443), it has been shown that acetates of benzylamine and ethylbenzylamine are superior to ammonium acetate and piperidine acetate in effecting the condensation of various ketones with ethyl cyanoacetate and that it is not unlikely that catalysts of ammonium acetate and benzylamine acetate type may have a mode of action which is dissimilar to that of secondary amines or other strongly basic catalysts like sodium ethoxide. Piperidine, however, is a stronger base than ethylbenzylamine, and as such should be a more efficient catalyst than ethylbenzylamine in base-catalysed condensations of Knoevenagel and related types (cf. Hauser and Breslow, *J. Amer. Chem. Soc.*, 1939, **61**, 795; Hauser and Renfrow, *ibid.*, 1937, **59**, 1823). This has actually been found in the case of the condensation of ethyl malonate and cinnamaldehyde. Whereas in the presence of piperidine, a 70% yield of the condensation product was readily obtained, practically no reaction occurred when "ethylbenzylamine" was used as a catalyst (cf. Aspinall and Baker, *J.Chem.Soc.*, 1950, 745). This is in striking contrast to the results described in Part I (*loc. cit.*).

"Promotor" effect of Primary Amines.—It was thought that traces of benzylamine which were likely to contaminate the ethylbenzylamine, as prepared by the procedure of Pinner and Franz (*Ber.*, 1905, **38**, 1548), might be responsible for its enhanced efficiency in effecting the condensations of ketones with ethyl cyanoacetate. Of course, this implies that these condensations can proceed by a route other than that followed by other Knoevenagel reactions (e.g. the condensations of aldehydes with malonic ester). This has been confirmed by the finding that benzylamine-free ethylbenzylamine is in fact a much less efficient catalyst than piperidine. In a number of cases investigated, reactions of various ketones (acetophenone, methyl-*n*-hexyl ketone, etc.) with ethyl cyanoacetate in the presence of pure ethylbenzylamine were slow and incomplete. Addition of a trace of benzylamine, however, accelerated the reaction. Similarly, the addition of a trace of benzylamine to piperidine-catalysed reactions had a pronounced effect on the rate of the reaction (Table I).

This effect of benzylamine is also clearly illustrated in the condensation of the keto-esters (I), (II) and (III) (Table II) with ethyl cyanoacetate. The yield figures shown in the 1st column are those obtained, when piperdine is employed as a catalyst; the second column gives the percentage yield when some benzylamine is also added.

TABLE I

No.	*Ketone.	†Catalyst.	Time.	Yield.
1	Acetophenone	Ethylbenzylamine (A)	12 hrs.	25.0%
		Piperidine (B)	55	74.0
		A+benzylamine	8	74.0
		B+benzylamine	7	74.0
2	Methyl-*n*-hexyl ketone	A	10	30.0
		B	18	89.6
		A+benzylamine	8	87.0
		B+benzylamine	6	90.0

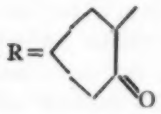
* 0.1 *M* of ketone, 0.1 *M* of ethyl cyanoacetate.

For acetophenone 0.01*M* of A or B and when benzylamine (0.001 *M*) is also added 0.009 *M* of A or B. For the second ketone, half of these quantities.

Benzylamine itself is a good catalyst for these condensations (cf. Part I, *loc.cit.*). But in the presence of a secondary amine it appears to play a different role. For example, the keto-ester (III) gives an abnormal product when only benzylamine is employed, whereas the combination piperidine (or ethylbenzylamine) + benzylamine gives the expected product. The condensations of these keto-esters with ethyl cyanoacetate have been carried out in connection with some synthetic investigations in the azulene and sesquiterpene series, and the experimental details will be published in the appropriate forthcoming publications.

Some Unusual Factors Influencing the Yield.—Under the same set of experimental conditions of this reaction, different ketones may behave differently, depending on the reactivity of the carbonyl group. Two important factors influence the latter, viz., the electrical influences and the inter- and intramolecular geometry of the molecule. Table II shows the effect, which the length of the ester side-chain as well its structures produces on the yield of the condensation product. Apparently, it is difficult to visualise any sort of electron shifts which can possibly explain this difference in behaviour. A possible explanation can be sought in the other factors, which govern the intramolecular forces and restrict rotations about the single carbon-carbon bond from the energetics point of view (cf. Prelog, *J. Chem. Soc.*, 1950, 420; Kuhn, *J. Chem. Phys.*, 1947, **15**, 843; Brown, Fletcher and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212). This will make certain constellations (conformations) of these molecules preferable over the others. It is quite likely that in the keto-esters (II), (III) and (IV), the preferred constellations are such which hinder the approach of the attacking anion to the carbonyl group. It is apparent that the presence of a methyl group on the carbon atom next to the ring has a strong deactivating influence on this reaction and probably the methylene group next to the ring is involved in hindering the carbonyl, the extent of hindrance becoming enlarged, when one of its hydrogens has been replaced by a methyl group. At present nothing more can be said about the configuration of these preferred constellations besides the point that those constellations will be more stable in which the interatomic repulsions are the least (e.g. cf. the constellation of declain, Barton, *J.Chem.Soc.*,1948, 340).

TABLE II



No.	Keto-ester.	Yield (%).	
I	R-CH_2.COOEt	55	89
II	R-CH(-CH_3).COOEt	3-5	27
III	R-CH_2.CH_2.COOEt	20	43
IV	R-CH(-CH_3).CH_2.COOEt	<1	2-5
V	R-CH_2.CH_2.CH_2.COOEt		64*

* Yield reported by Sörm (*Coll. Czech. Chem. Comm.* 1947, **12**, 251). Under the same conditions (IV) gave less than 1% yield.

Role of the Solvent.—The chief role of the solvent in the procedure of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452) for carrying out such condensrtion is to act as an entrainer for the water formed in the reaction. For the condensation of water-soluble volatile ketones, benzene is evidently useless and Wideqvist (*Acta Chem Scand.*, 1949, **3**, 303) has used $CHCl_3$ for the removal of the water azeotropically. Other solvents like CCl_4, toluene, etc. have also been employed for the purpose (cf. *Chem. Abst.*, 1949, **43**, 7507). Cragoe, Robb and Sprague (*J. Org. Chem.*, 1950, **15**, 381) have studied the effect of the solvent on the condensation of benzophenone with ethyl cyanoacetate.

Table III records the percentage yields of the condensation products of ethyl cyanoacetate with the keto-ester (III), when the solvent is varied. The catalyst used is "ethylbenzylamine". The results are rather unexpected.

TABLE III*

Ethyl cyclo*pentylidene-cyanoacetate-2-propionate.*

No.	Solvent.	Time.	Yield.
1	Benzene	4-5 hrs.	40-45%
2	$CHCl_3$	20	57
3	Petroleum ether (30°-50°)†	24	71
4	CH_2Cl_2	30	75

* 0.1 *M* of the keto-ester, 0.11 *M* of ethyl cyanoacetate and 0.01 *M* of the catalyst.
† Reaction mixture not homogeneous.

As is apparent, the lowest boiling solvent gives the best yields, though the rate of the reaction is low as anticipated. Both the reactants as well as the product (unsaturated cyano-ester) contain polar groups and it is unlikely that the solvent can have any effect on the thermodynamic probability of the reaction due to any appreciable difference in the

solvation of products and the reactants. However, a temperature effect is quite apparent. If this particular reaction is carried out at 0° for several days in the presence of piperidine, a 33% yield of the condensation product can be realised (Cook and Linstead, *J.Chem. Soc.*, 1934, 953). However, using the same catalyst and employing C_6H_6 as the entrainer, the yield is only 20%. No possible explanation is put forward at present, as the necessity of a detailed investigation on this unexpected effect of the solvent (temperature?) is apparent.

Experimental

Ethylbenzylamine.—The reaction of ethyl bromide with benzylamine was carried out essentially as described in Part I (*loc. cit.*) but the time of reaction was increased from one week to three weeks at room temperature (20°-25°). The product was purified by fractionation through 6″ fractionating column packed with glass helices (single turn) and topped with a total-condensation variable take-off-type stillhead (Fig. 1). The purified material had b. p. 193°-195°/684 mm.

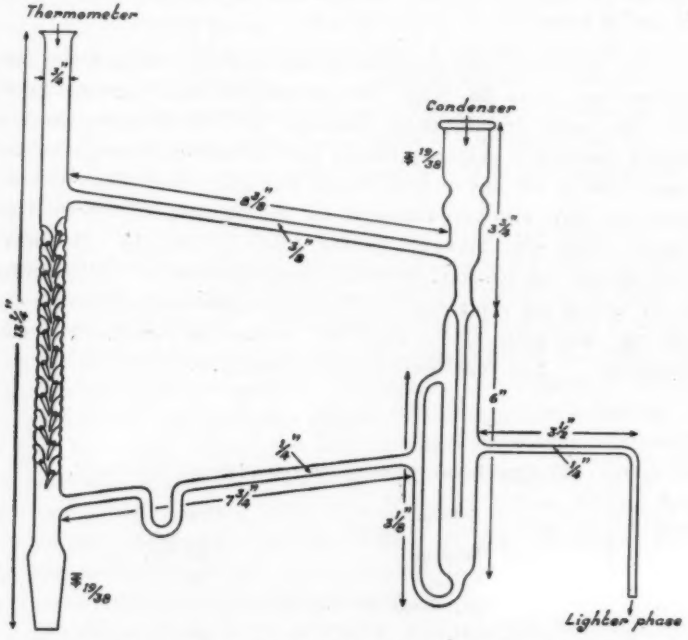


Fig. 1. For reaction in which the entrainer is haevier than water.

General Directions for the Choice of the Catalyst

(*a*) For unhindered aliphatic and alicyclic ketones, benzylamine is the catalyst of choice (0.003 *M* for 0.1 *M* of the ketones).

(*b*) For alkylaryl ketones the proportion of the catalyst should be increrased to 0.01*M*; and for purely aromatic ketones, 0.02*M* of the catalyst, added in two or three lots

after suitable intervals (it is best to make the successive addition, as the reaction slows down).

(*c*) For hindered ketones, ammonium acetate is the preferred catalyst (Cragoe *et al.*, *loc. cit.*).

(*d*) For ketones carrying other functional groups (e.g. keto-esters) it is best to use a combination of piperdine (0.009*M*) and benzylamine (0.001*M*), as the formation of any possible by-products is apparently suppressed.

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ON THE RELATIONSHIP BETWEEN FLUIDITY AND SURFACE TENSION OF LIQUIDS

By Asoke Kumar Mukherjee

An equation connecting fluidity of a liquid with its surface tension has been deduced from considerations of free volume in the liquid state. The equation appears to be more liberal in its outlook than Newton Friend's empirical equation for the same.

Literature records very little attempt in rationally connecting surface tension of a liquid with its viscosity. Different empirical relations have been proposed by a number of workers like Silverman and Roseveare (*J. Amer. Chem. Soc.*, 1932, **54**, 4460), Buehler (*J. Phys. Chem.*, 1938, **42**, 1207), Tripathy (this *Journal*, 1942, **19**, 51), Newton Friend (*Nature*, 1942, **150**, 432; *Phil. Mag.*, 1943, **34**, 643) and others. Of these the equation proposed by Friend has been found to have a wider applicability and has generally been accepted as the best guide in the case of normal liquids. Investigations of Chakravarty (this *Journal*, 1946, **23**, 243) in recent years have also corroborated the general validity of Friend's equation.

The equation proposed by Friend as late as 1942 connects the two entities, surface tension and viscosity of a liquid, when both of them change due to changes of temperature by the relation

$$\gamma = k.\sqrt{\eta} \qquad \ldots \quad (1)$$

where γ represents surface tension and η, the coefficient of viscosity and k, a constant. Taking logarithms of both sides of (1)

$$\log \gamma = \log k + \tfrac{1}{2} \log \eta \qquad \ldots \quad (2)$$

which represents a linear relationship between $\log \gamma$ and $\log \eta$.

Experimental results corroborate this linear relation for numerous liquids as evident from the literature. A closer scrutiny of equation (2) reveals that these graphs should not only be straight lines but they will all have the same slope equal to $\frac{1}{2}$, and so they should all be parallel, irrespective of the nature of the liquid. The intercept $\log k$ will only differ from one liquid to another. But such parallelism of the graphs drawn for different liquids on the same scale in one graph cannot obviously be observed, as will be evident from Figs. 1 and 2 where graphs for a number of liquids have been shown from data worked out in this laboratory. Evidently Friend's equation is not so satisfactory as it was at first supposed to have been.

There is therefore room for further investigation along this line, specially because all the existing relationships are more or less empirical. The present investigation reports such an attempt.

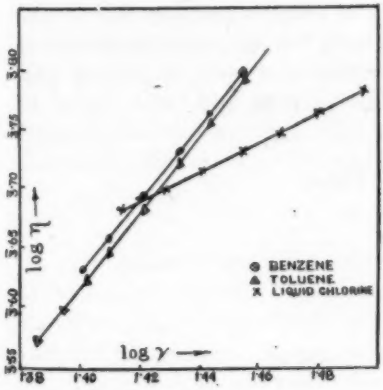

FIG. 1

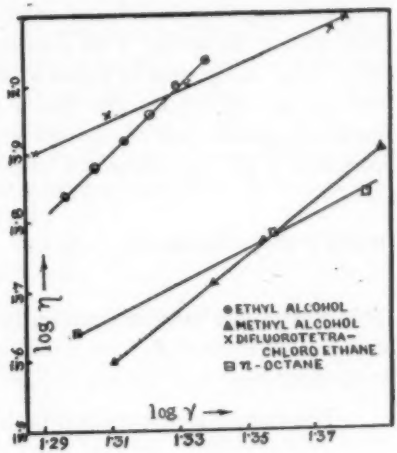

FIG. 2

Equation connecting Viscosity and Surface Tension

The manner in which the fluidity of a liquid has been connected by the author with its free energy (vide Mukherjee, this *Journal*, 1951, **28**, 519) appears to be promising in opening up new relations between viscous properties of a liquid with its different physical properties, some of which have been published in previous communications. Surface energy forms a part of the free energy of the liquid state. Consequently it may be visualised that fluidity may in a like manner be connected with surface energy and thence with surface tension. But the procedure is complex. For this reason, instead of passing directly from free energy to surface tension, the whole problem has been discussed from the fundamental aspect of free volume in liquids, an idea previously proposed by the author (*ibid.*, 1949, **26**, 493), through the help of which fluidity has been connected with surface tension.

It is well known that surface tension is due to a pull exerted on the molecules residing at the surface of a liquid by molecules in the bulk, as a result of which the surface molecules tend to pass into the interior, thereby creating a tendency on the part of the liquid surface to contract. Let us imagine two contiguous layers of molecules just at and near the liquid surface (Fig. 3). The attractive pull exerted on the surface layer (A) by the contiguous layer (B) is determined by the distance between the two layers and varies inversely as some power of the distance depending on the nature of the liquid molecules. Thus, it is well known that the interaction energies in polar and non-polar molecules are different functions of their distance apart. It is possible to represent these attractive forces as

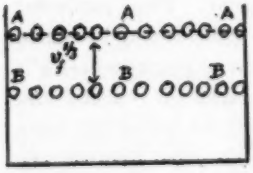

FIG. 3

$$F \propto \frac{1}{r^{n'}} = \frac{k}{(v_f^{\frac{1}{3}})^{n'}} \qquad \ldots \quad (3)$$

where F stands for the force of interaction, r, the distance between molecules, v_f, for the free volume as usual, k for a constant and n', for an integer. Substitution of $v_f^{\frac{1}{3}}$ for r rests on the assumption of a cubical structure of the liquid which is generally true in the case of normal liquids, and hence, justified in those cases. Again, under conditions of moderate pressure and at ordinary temperature, the fluidity of a liquid is directly proportional to the free volume (cf. Mukherjee, this *Journal*, 1951, **28**, 363).

$$\phi = A.v_f \qquad \ldots \quad (4)$$

where ϕ stands for fluidity $(1/\eta)$ and A is a constant. Hence

$$v_f = \phi/A.$$

Substituting this value in equation (3)

$$F = \frac{k}{[(\phi/A)^{\frac{1}{3}}]^{n'}}.$$

This force F is proportional to the surface tension (γ) and so

$$\gamma = \frac{k.k'.A^{n'/3}}{\phi^{n'/3}} = kk'A^{n'/3}.\ \eta^{n'/3} = K.\eta^{n'/3} \qquad \ldots \quad (5)$$

where k' stands for the proportionality constant between F and γ and K stands for the constant term $(k.k'.A^{n'/3})$. Taking logarithm on both sides of (5)

$$\log \gamma = \log K + n'/3 \log \eta \qquad \ldots \quad (6)$$

This equation is essentially similar to that of Friend (equation 2) but differs only in the magnitude of the solpe. Instead of being universally equal to $\frac{1}{2}$ for all liquids it is given by $n'/3$. The value of n' will depend on the nature of the interaction force, as already stated. The nature of the intercept $(\log K)$ (in equation 6) is determined by k, k' and A, in which A is certainly known to be dependent on the nature of the liquid. Thus, in equation (6) both the intercept $(\log K)$ and the slope $(n'/3)$ depend on the nature of the liquid. In this respect equation (6) appears to be more liberal than that of Friend (equation 2). Moreover, it is interesting to note that equation (6) also refers to temperature changes alone. Changes in ϕ due to factors other than temperature, e.g., due to pressure, is given by

$$\phi = A.v_f^n$$

instead of $\phi = A.V_f$ (vide Mukherjee, *ibid.*, 1951, **28**, 363).

Another advantage of equation (6) is that it gives an idea about n' which determines the magnitude and nature of interaction between molecules in a liquid. This particular point will be more fully discussed in some furture communication. But it may be stated here at least qualitatively that parallelism should be expected between graphs where n''s are the same for the two liquids. This will be evident from the cases of benzene and toluene, both of which are non-polar in nature and in both cases the interaction force between molecules, *i.e.*, the internal pressure, is of the same type, viz., that between two induced dipoles. As a matter of fact, it is known that a mixture of benzene and toluene obeys Raoult's law with sufficient accuracy and behaves like ideal mixtures where the internal pressures are almost equal. In such a case we can expect an approximate parallelism between $\log \gamma$ and $\log \eta$ graphs for the two according to equation (6), which is

obvious from Fig. 1. (data worked out in this laboratory). If, however, the two liquids are of entirely different nature, the values of n' will differ and the slopes are expected to differ also. This is also shown in Fig. 1 where the graph for liquid chlorine has been shown to intersect the graphs for benzene and toluene (data from Landolt-Bornstein Tabellen, 1935). Another example to illustrate this point has been presented in Fig. 2 in which ethyl and methyl alcohols being liquids of similar nature show parallel rectilinear graphs, whereas the graphs for difluorotetrachloroethane (data taken from Landolt-Bornstein Tabellen, 1935) intersect those of the alcohols.

EXPERIMENTAL

The measurements of viscosity and surface tension were carried out in an electrically controlled air thermostat closed on all sides with double walls of asbestos excepting in the front which was closed with double glass doors. Temperature was maintained constant within $\pm 0.2°$.

Viscosity was measured with the help of a standard Ostwald viscometer (No. 0) for which 212 secs. were required for the flow of water. Densities of the liquids were determined as usual with pyknometers of capacity about 30 c.c. This was measured up to the tenth of a second. Absolute viscosity was determined from a knowledge of viscosity of water.

Surface tension was measured with the help of Du Nouy's tensiometer which reads up to 0.05 dyne. The liquid was placed inside the thermostat till it attained the desired temperature and the surface tension was measured by manipulating the apparatus from outside by some improvised methods.

The liquids used were all of "Analar" or "Guaranteed Reagent" quality. Dioxane and *cyclo*hexane were distilled twice. Data are shown in Table I. All other data were collected from Landolt-Bornstein Tabellen (1935).

TABLE I

Benzene.			Toluene.			Dioxane.		
Temp.	η. (poise).	γ. (dynes).	Temp.	η. (poise).	γ, (dynes).	Temp.	η_3 (poise).	γ. (dynes).
25°	6.06	28.2	35°	5.00	26.5	25°	1.150	34.75
30°	5.62	27.5	40°	4.68	26.0	30°	1.055	34.05
35°	5.25	26.9	45°	4.42	25.5	35°	0.997	33.30
40°	4.90	26.3	50°	4.17	25.1	40°	0.912	32.50
45°	4.57	25.7	55°	3.93	24.7	45°	0.836	31 70
50°	4 27	25.1	60°	3.72	24.3	50°	0.785	30.90
*cyclo*Hexane.			Carbon tetrachloride.			Ethyl alcohol.		
30°	8.22	25.4	25°	8.90	25.95	25°	12.0	21.8
35°	7.63	24.7	30°	8.32	25.20	30°	10.0	21.4
40°	7.05	24.0	35°	7.86	24.70	35°	9.12	21.0
45°	6.54	23.2	40°	7.36	24.10	40°	8.32	20.65
50°	6.07	22.6	45°	6.95	23.55	45°	7.59	20 20
55°	5.65	22.0	50°	6.58	23.10	50°	6.92	19.80
60°	5.28	21.5						

2—1831P—10

All these data excepting those of benzene and toluene are represented in Figs. 4 and 5.

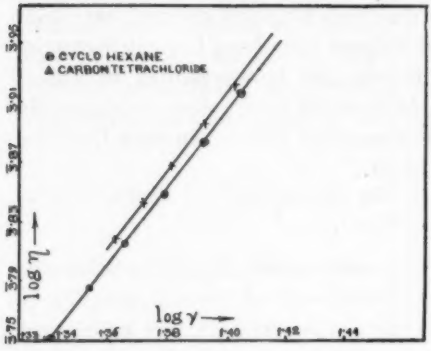

FIG. 4

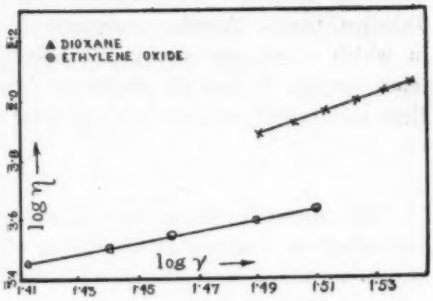

FIG. 5

The author's thanks are due to Prof. S N. Mukherjee for his help and guidance and also to the authorities of the College of Engineering and Technology, Calcutta for allowing him the use of their library and laboratories.

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COMPOSITION OF PERIODATES. PART I. BISMUTH PERIODATE

By James W. Neckers and Robert A. Hernandez

The composition of bismuth periodate, precipitated by two different methods and dried at several different temperatures, has been determined. The product obtained by drying at room temperature appears to be of uncertain and variable composition. At 80° and 110° the Bi/I ratio is 3:2, indicating that the compound may be a basic mesoperiodate or an acid paraperiodate, depending on the p_H of the medium used. This does not confirm previously reported work by two other workers.

In the search for a volumetric method for the determination of bismuth, the reported insolubility of bismuth periodate in dilute acids (Willard and Thompson, *J. Amer. Chem. Soc.*, 1934, **56**, 1827) suggested a possibility. But after numerous trials under a variety of conditions, no semblance of reproducibility was obtained by the method used. This suggested the necessity of an investigation regarding the composition of the bismuth periodate precipitate.

Three reports have been made concerning the nature of this compound. Raychoudhury (this *Journal*, 1941, **18**, 576) adding $Na_3H_2IO_6$ to $Bi(NO_3)_3$ in a nitric acid solution and drying the precipitate at room temperature over concentrated H_2SO_4, reported a product with the composition of Bi_2O_3. $2I_2O_7$. H_2O. He also suggested (*Science & Culture*, 1941, **7**, 57) $3Bi_2O_3$. I_2O_7. $7H_2O$. More recently Bombelli (*Anal. assoc. quim. Arg.*, 1949, **37**, 279) reported different results using KIO_4 in 50% acetic acid solution and drying the precipitate at 100°. He proposed $Bi_5(IO_6)_3$. $4H_2O$ as the formula for the product under those conditions.

It is evident that the stoichiometry of the compound is complicated by the existence under varying conditions of several periodate radicals and the well known proclivity of bismuth to form basic compounds. The H_2O reported may also be present as water of constitution or water of hydration. With those points in mind, it was decided to attempt to determine the composition of the product under different conditions of precipitation and of drying.

Considerable difficulty was encountered in developing a procedure that would give a reproducible product. First, a dilute solution of KIO_4 was used as the precipitating agent, adding it to a slightly acid solution of bismuth nitrate. Extended drying periods were necessary to produce a constant weight, resulting in products that yielded inconsistent analyses. Washing the precipitate with alcohol and with acetone was tried to assist in the removal of moisture, but small amounts of the organic reagents apparently remained absorbed, even after persistent aeration. This was evidenced by the reduction of some of the periodate on standing, as shown by the product assuming a tan colour. The possibility of potassium ion being a contributor to the variable nature of the precipitate led to the decision to use a solution of periodic acid which would add no metallic cations. More consistent results were obtained. Later it was also learned that the product could not be dried consistently over anhydrous $CaCl_2$. This probably is due to a lower vapour pressure of dried bismuth perio-

date than that of the $CaCl_2$ used. Anhydrous $Mg(ClO_4)_2$ was used as a more satisfactory desiccant in most of the final cases.

Series of determinations were made at room temperature (25°), 80°, 110°, 150° and 250°. The product was dried to a constant weight at room temperature in a vacuum desiccator over concentrated H_2SO_4. At the other temperatures the product was alternately heated for two hours in a drying oven, with control of ± 1°, and cooled in a desiccator over anhydrous $Mg(ClO_4)_2$. The bismuth periodate was found to be very hygroscopic and 6 weeks of drying at room temperature or from 6 to 10 heatings were necessary to produce a constant weight.

Two methods of preparation were used, one from a solution containing an excess of bismuth ion (Method A) and the other from a solution containing an excess of periodate ion (Method B), under different conditions of acidity. Typical results are listed in Table I.

Experimental

Reagents: *Bismuth Nitrate*.—Approximately 25 g. of "Merck Reagent Bismuth Subnitrate" were dissolved in 125 ml. of 6*N*-HNO_3 and diluted to one litre. Gravimetric analysis by the phosphate method (Blasdale and Parle, *Ind. Eng. Chem. Anal. Ed.*, 1936, **8**, 352) showed that the 25 ml. pipette, used for all the bismuth samples, delivered 0.2955 g. of Bi^{3+} from this stock solution.

Periodic Acid.—G. Frederick Smith Chemical Co. Reagent H_5IO_6 was used in a solution of approximately 40 g. per litre.

Standard Sodium Thiosulphate.—Eimer and Amend Reagent $Na_2S_2O_3$, $5H_2O$ was made up to approximately 0.1*N* and standardised against Baker's A. C. S. Standard $KBrO_3$ (99.8+% assay) by the indirect iodimetric method.

Potassium Iodide.—Eimer and Amend Reagent KI was used in the standardisation of the sodium thiosulphate and for the determination of the periodate in the bismuth periodate analysis.

Procedure: *Method* (*A*).—One 25 ml. pipetteful of the stock bismuth nitrate solution and 5 ml. of 6*N*-HNO_3 were diluted with distilled water to approximately 300 ml. in a 600 ml. beaker. This solution was heated nearly to boiling and 25 ml. of the stock periodic acid solution (an excess) were added slowly with stirring. One drop of the periodic acid was sufficient to start precipitation of the bismuth periodate. The precipitate was digested on a hot plate for 2 hours. The mixture was allowed to cool overnight and then filtered through a porcelain filtering crucible (Selas No. 2001, fine). The p_H of the filtrate, without washings, was approximately 1.4 as measured by a Coleman, Model 3D, p_H meter. The precipitate was washed by decantation at least 4 times with 50 ml. portion of distilled water containing 1 ml. of dilute HNO_3, and was dried to a constant weight. The precipitate had a very light green colour, was bulky and gelatinous, but under the above conditions settled rapidly. Drying produced a light green compact disk in the bottom of the crucible. One set of samples in quadruplicate was dried at room temperature (25°) in a vacuum desiccator over fresh, concentrated H_2SO_4. Other samples in quadruplicate were also dried in a drying oven at 80°, 110° and 150°.

Method (*B*).—To give a different set of conditions for the formation of the bismuth periodate, 40 ml. of the stock periodic acid solution with 70 ml. of 6*N*-HNO_3 were measured into a 600 ml. beaker and 25 ml. of the stock bismuth solution were added. No precipitate formed. Approximately 100 ml. of distilled water were added with the formation of a slight cloudiness in the solution, which disappeared on heating. The p_H of the solution was approximately 0.3. Dilute NH_4OH solution was added slowly with stirring to cause precipitation and in sufficient quantity to bring the p_H up to the approximate 1.4 value of Method A. At this point precipitation appeared to be complete as shown by subsequent tests on the filtrate. Filtration, washing and drying procedures, at room temperature and at 110°, were the same as in Method A. The precipitate had the same appearance as that obtained in Method A, but was more finely divided and more difficult to filter. The dried product, however, was much more readily reactive with dilute HCl than that obtained by Method A. The possible significance of that is discussed later.

Analysis of Product: *Bismuth*.—The amount of bismuth in the product was assumed to be 0.2955 g., taken from the analysis of the stock solution, and assuming its complete precipitation as indicated by the cloudiness produced by the first drop of periodate and also by obtaining no further precipitation on neutralisation of the filtrate. Several methods were tried for the determination of the bismuth in the product without success. If it were dissolved in a concentrated HNO_3 and then phosphate and NH_4OH added, some bismuth was precipitated as periodate. If the periodate were first decomposed with HCl, the $BiPO_4$ was contaminated, probably with basic iodide, as the $BiPO_4$ had a tan or yellow colour on ignition. Ignition at 500° of the bismuth periodate, supposedly to Bi_2O_3, gave variable results, as did attempts to obtain BiOCl by rapid dilution of the solution obtained by putting the periodate into solution with concentrated HCl. In all cases iodide or basic iodide caused contamination and repeated evaporations with concentrated HNO_3 were also unsuccessful in removing all of the iodide.

Periodate.—A weighed portion of the dried bismuth periodate was covered with distilled water in a 400 ml. beaker and 3 g. of KI in water solution were added. No reaction occurred. Dilute HCl was then added slowly, causing interaction, with the dissolution of the periodate and the quantitative liberation of iodine. The iodine was then titrated with the standard $Na_2S_2O_3$ solution, using freshly prepared starch as the indicator. The burette used had been standardised by the U. S. Bureau of Standards. The end-point was stable and the titration was routine, except that the choice of the point at which the starch should be added required some experience as the disappearance of the colour of the dissolved iodine was masked somewhat by the similar colour of the BiI_4^- present in the solution (Meites, *Anal. Chem.*, 1952, **24**, 1620).

Water.—The percentage of H_2O was taken by difference after converting Bi to Bi_2O_3 and I to I_2O_7. This left undetermined whether the water is water of constitution or of hydration.

TABLE I

Average analyses of bismuth periodate.

Drying temp.	% Bi.	% Bi_2O_3.	% I.	% I_2O_7.	% H_2O.	Bi/I ratio. Weight.	Atomic.
			Method A.				
25°	56.31 ± 0.02	62.78	23.89 ± 0.02	34.44	2.78	2 36	1.43
80°	57.30 ± 0.10	63.91	22.97 ± 0.01	33.10	2.99	2.49	1.51
110°	57.47 ± 0.03	64.10	22.65 ± 0.02	32.60	3.30	2.54	1.54
150°				30.47			
200°				28.78			
			Method B.				
25°	55.46 ± 0.12	61.50	24.30 ± 0.12	35.08	3 15	2.28	1.38
110°	57.21 ± 0.07	63.78	23.18 ± 0.01	33.34	2 88	2 47	1.50

DISCUSSION

The atomic ratios of bismuth to iodine, shown in Table I, yield the possible formulas of the composition listed in Table II.

TABLE II

Proposed formulas for bismuth periodate.

No.	Temp.	Method.	Bi/I ratio.	Formula.	Theoretical. %Bi.	%I.
1	25°	A	1.43	$Bi_{10}O(HIO_6)_7.2H_2O$	56 34	23.95
				or		
2				$Bi_{10}(OH)_9(IO_5)_7.H_2O$		
3	25°	B	1.38	$Bi_4(HIO_6)_3.1\frac{1}{2}H_2O$	54.47	24.82
				or		
4				$Bi_4(OH)_3(IO_5)_3.1\frac{1}{2}H_2O$		
5	80°	A	1.51	$Bi_3(OH)_3(IO_5)_2$		
6	110°	A	1.54			
7	110°	B	1.50	$Bi_3(OH)(HIO_6)_2$	57 43	23.25
				or		
8				$Bi_3(HIO_6)(IO_6).H_2O$		

The results at 80° and at 110°, all point to a 3: 2 ratio. Both methods, starting with excess bismuth and also with excess periodate, confirm this. It is possible that the basic mesoperiodate of Formulas 5 and 6 (Table II) is the product of precipitation at p_H 1.4, while the acid paraperiodates of Formula 7 or 8 are the products from the strongly acid media with p_H 0.3 of Method B. That there is a different compound is indicated by the distinctly greater reactivity with dilute hydrochloric acid of the bismuth periodate that is precipitated from a strongly acid solution. The lower reactivity of the product from Method A would seem to indicate the possibility of a basic bismuth salt.

No clear-cut formula results from the products at room temperature by either Method A or B. The 1.43 ratio giving 10:7 and the 1.37 ratio giving 11:8 as the Bi:I relationships probably indicate a mixture of uncertain composition.

The relatively small change in water content (calculated by difference) between the products dried at 25° up to 110° probably indicates that the HOH is present chiefly as "water of constitution" rather than "water of hydration". The calculated formulae show this involvement.

The Bi/I weight relationships, listed in Table I as ranging from 2.28 to 2.54, are given for comparison with those of Raychoudhury (*loc. cit.*) and of Bombelli (*loc. cit.*). The values by Methods A and B confirm Raychoudhury's ratio of 2.31, but not his formula, for the composition of bismuth periodate at room temperature. Bombelli's lower iodine content (21.16%) gives a higher ratio (2.69) with approximately the same percentage of bismuth (57.03) as reported here.

Evidence of the instability of bismuth periodate with rising temperature above 110° is shown by the lower percentage of periodate at 150° and 200° listed as I_2O_7 in Table I. The tan to brown colour of the product is a further evidence of such decomposition.

Like lead periodate (cf. Willard and Thomson, *loc. cit.*) the composition of bismuth periodate is dependent on the conditions of precipitation, particularly on the p_H of the medium used and the temperature of drying. Both basic mesoperiodates and acid paraperiodate appear to be possible. At room temperature particularly, the product is of uncertain formulation.

The authors are indebted to former students at Southern Illinois University, particularly Aubrey Montgomery, Charles W. Blessin, William Ulrich, and Bruce Kirkman for much preliminary experimentation that led to the final methods used in this work.

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VISCOSITY OF UNIMOLECULAR FILMS

By Asoke Kumar Mukherjee

The viscosity of a unimolecular liquid film has been connected with its surface pressure. An equation similar to that proposed by Eyring has been arrived at from different considerations.

The viscosity of unimolecular films of liquids owes its importance to the problem of lubrication. Boyd and Harkins (*J. Amer. Chem. Soc.*, 1939, **61**, 1188) proposed an empirical relationship between the viscosity and surface pressure of unimolecular films by the equation

$$\log \eta = a + b.p \qquad \ldots \qquad \ldots \qquad \ldots \quad (1)$$

where η stands for the viscosity coefficient of the unimolecular film with surface pressure p, and a and b are constants.

Eyring (vide Glasstone, Laidler and Eyring, "The Theory of Rate Processes", Mc Graw Hill Book Co., 1941) has attempted to impart a theoretical basis to the above equation in the light of the 'hole' theory of liquids proposed by him and has deduced an equation connecting the two, of the form

$$\ln \eta = \ln \eta_0 + p.\frac{\Delta A}{RT} \qquad \ldots \qquad \ldots \quad (2)$$

where η_0 represents the surface viscosity at zero pressure obtained by extrapolation of its values at significant surface pressures and ΔA stands for the expansion of the surface area per molecule in the excited state necessary for the viscous flow. He is of opinion that "if ΔA be taken as constant for a given substance and independent of pressure, as will probably be the case over a considerable range of pressure, it follows that

$$\ln \eta = \ln \eta_0 + p.c \qquad \ldots \qquad \ldots \qquad \ldots \quad (3)$$

where c is a constant".

This assumption that there should be an expansion for the attainment of an excited state which, according to Eyring, is so much necessary, appears to be more or less arbitrary and awaits experimental verification. Another assumption, that ΔA should in the case of 1 g. mole be exactly equal to the area of cross-section of N molecules, where N stands for the Avogadro's number (*i.e.* on being excited the cross-section of each molecule doubles itself), appears to be arbitrary, although on this assumption the calculated value of the constant c has been shown to be in agreement with the experimental value obtained by Boyd and Harkins (*loc. cit.*).

In the present paper it is proposed to arrive at a relation connecting η with p (surface pressure) from an entirely different approach without any of the assumptions made by Eyring, but from the point of view of free energy changes in such processes.

The New Outlook

From the picture of the liquid state of aggregation, as presented by the author (this *Journal*, 1949, **26**, 493) and from the fact that the fluidity of a liquid (reciprocal of the coefficient of viscosity) varies linearly with the free volume of liquids (cf. Mukherjee, *ibid.*, 1951, **28**, 519), the equation proposed for the fluidity of a liquid is

$$\phi = \frac{NAh^3}{(2\pi mkT)^{3/2} f_v . f_r} \cdot e^{(\Delta E_v - G)/RT} \quad \ldots \quad \ldots \quad (4)$$

At constant temperature the equation can be simplified to

$$\phi = B. \exp. (-G/RT) \quad \ldots \quad \ldots \quad \ldots \quad (5)$$

where B stands for the constant term

$$\frac{NAh^3 \; e^{\Delta E_v/RT}}{(2\pi mkT)^{3/2} f_v f_r}$$

and the other terms have their usual significance, G standing for the Gibb's potential or free energy. Changing φ to $1/\eta$

$$\ln \eta = -\ln B + G/RT \quad \ldots \quad \ldots \quad \ldots \quad (6)$$

and differentiating this at constant temperature

$$d \ln \eta = d\, G/RT \quad \ldots \quad \ldots \quad \ldots \quad (7)$$

We can apply this equation to the case of surface pressure if we can evaluate dG in such cases.* From thermodynamic consideartions

$$dG = -S.dT + V.dP$$

whence at constant temperature

$$dG = V.dp \quad \ldots \quad \ldots \quad \ldots \quad (8)$$

This equation needs modification in the case of surface pressure which is a pressure in two dimensions and is expressed as force per unit length. In this case

$$dG = A.\, dp \quad \ldots \quad \ldots \quad \ldots \quad (9)$$

where A is the surface area of the film and dp, the change in surface pressure. Equation (9) may be shown to be dimensionally valid. By substituting (9) in (7) we get

$$d \ln \eta = \frac{A.\, dp}{RT} \quad \ldots \quad \ldots \quad \ldots \quad (10)$$

Integration of (10) will lead to the expected relation between η and p. But the integration can be carried out if only we know the relation between A and p.

This $A.dp$ is analogous to $V.dp$ in equation (8). While considering the effect of external pressure on viscosity (Mukherjee, *Trans. Indian Inst. Chem. Eng.*, 1950, **2**, 36)

* This equation, as already mentioned, has been based on the relationship $\phi = A.\, v_f$, where v_f stands for the free volume in liquids. This is justified only at low and moderate pressures and moderate temperatures (vide Mukhejree, *Trans. Indian Inst. Chem. Eng.*, 1950, **2**, 36) and can be applied to the case of surface pressures at ordinary temperatures on the ground that surface pressure seldom assumes very high values.

the relationship of v with p was worked out through the changes in the compressibility coefficient (β) with pressure by the help of Tait's equation. In the present case no such relation exists connecting change of compressibility coefficient of a liquid film with surface pressure.

(*i*) *A independent of p.*—Fortunately, however, there is no need for considering such a change in this case because variations of surface pressure do not extend so widely as to affect the coefficient of compressibility in a majority of cases. The area of a liquid film may be regarded as suffering little change with change in pressure. This point may be further understood from the diagrams relating surface pressure with area per molecule worked out by Adams ("The Physics and Chemistry of Surfaces", 2nd Ed., p. 47) from which it will be evident that condensed films exhibit practically no compression even at high pressures and the average cross-section per molecule may be regarded as constant (independent of pressure) with fair accuracy. In this case it is possible to integrate equation (10) between limits η_0 and η, where η_0 and η are the values of viscosity at $p = 0$ and $p = p$ respectively. By actual integration

$$\ln (\eta/\eta_0) = \frac{A}{RT} \cdot p$$

whence

$$\log \eta = \log \eta_0 + \frac{A}{2.303RT} \cdot p.$$

At constant T, $(A/2.303RT)$ is a constant ($= C$, say), whence

$$\log \eta = \log \eta_0 + C.p \quad \ldots \quad \ldots \quad (11)$$

This equation gives the required relationship and is of the same form as given by Boyd and Harkins (cf. equation 1). The value of C ($= A/2.303RT$) at 25°, assuming the value of A to be 21 sq. Å for a hydrocarbon chain, as given by Langmuir (*J. Amer. Chem. Soc.*, 1918, **40**, 361), comes up to 0.052 which lies within the experimental values of 0.022 to 0.076 in such cases (cf. Boyd and Harkins, *loc. cit.*). The equation is also identical with that of Eyring with this proviso that A stands for the area of cross-section of the molecules, and not the change in cross-section due to excitation.

In the above derivation A has been assumed to remain constant, which is amply justified by the investigations of Adam (*loc. cit.*) and Langmuir (*loc. cit.*), specially in the case of films over distilled water. It may be pertinent to mention here that Boyd and Harkin's work (*loc. cit.*) mainly refers to films on distilled water where an equation like (11) has been found to show good agreement.

(*ii*) *A varies with p.*—If, however, A does not remain constant but varies with p, integration of equation (10) can be carried out if A be known as a function of p. Such a relation has been indicated by Adam (*loc. cit.*) in the case of condensed films to be

$$A = A_0 (1 - \beta.p) \quad \ldots \quad \ldots \quad \ldots \quad (12)$$

where β is the compressibility coefficient of the film and is regarded as independent of pressure and A_0 stands for a constant representing the hypothetical value of A at $p = p$*

* The relation refers to condensed films only. For gaseous films the relation between A and p is known to be analogous to the ideal gas equation in two dimensions.

Substituting the value of A in $A.dp$, equation (10) can be put in the form

$$d \ln \eta = \frac{A_0 (1 - \beta p)\, dp}{RT} \quad \ldots \quad \ldots \quad \ldots \quad (13)$$

and integration carried out within limits of $p = 0$ and $p = p$

$$\ln (\eta/\eta_0) = \frac{A_0}{RT} (p - \tfrac{1}{2}\beta p^2)$$

or
$$\ln \eta = \ln \eta_0 + \frac{A_0}{RT} . p - \frac{1}{2} \frac{A_0}{RT} \beta p^2 \quad \ldots \quad \ldots \quad (14)$$

which is the required relationship.

This equation represents a conic and in order to check it with experimental data it should be reduced to a simplified form. If $(p - \frac{1}{2}\beta p^2)$ be put equal to x, then

$$\ln \eta = \ln \eta_0 + \frac{A_0}{RT} . x \quad \ldots \quad \ldots \quad \ldots \quad (15)$$

and plotting $\ln\eta$ against x, a straight line graph can be expected.

This equation has been verified with data taken from Joly's work (*J. chim. phys.*, 1947, **44**, 206) on surface films of palmitic acid on different concentrations of HCl solutions as reproduced in Tables I and II below.

TABLE I

Palmitic acid on $N/1000$-HCl at 17°.

p (dynes/cm.).	A (area/molecule).	η (abs.).
4	24.5 Å^2	1.9×10^{-4}
5	24.3	2.00
6	24.05	2.15
7	23.8	2.25
8	23.6	2.55
12	22.7	2.65
14	22.3	2.85

TABLE II

Palmitic acid on $N/100$-HCl at 25°.

p (dynes/cm.).	A (area/molecule).	η(abs.).
3	27.3 Å^2	1.12×10^{-4}
5	26.0	1.32
7	25.4	1.44
10	24.5	1.75
13	23.6	1.97
15	23.0	2.30
18	22.4	3.10

From the data on the second column of the tables [showing A (area/molecule)] the values of β have been calculated and the values of $\ln\eta$ from column 3, plotted against x according to equation (15), have been shown in Figs. 1 and 2 for $N/1000$- and $N/100$-HCl respectively. It will be evident from the graphs that they are linear and thus corroborate our point of view.

It may not be out of place to mention here that Joly's data did not fit in with equation (11) and it was naturally concluded that this was due to variation of surface area A which occurred in the cases studied by him. In support of this it may be worthwhile to refer to Langmuir's work (Langmuir and Schaefer, *J. Amer. Chem. Soc.*, 1937, **59**, 2400) in which it has been observed that when surface films are formed on the surface of solutions of electrolytes, there occurs appreciable adsorption of ions (specially cations) by the molecule constituting the film which has been confirmed by microphotographic studies. In such cases the nature of the film rightly becomes modified and viscosity shows "progressive changes due to adsorption of impurities" as Langmuir and Schaefer (*loc. cit.*) have themselves pointed out.

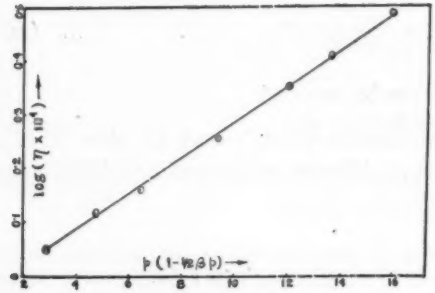

FIG. 1

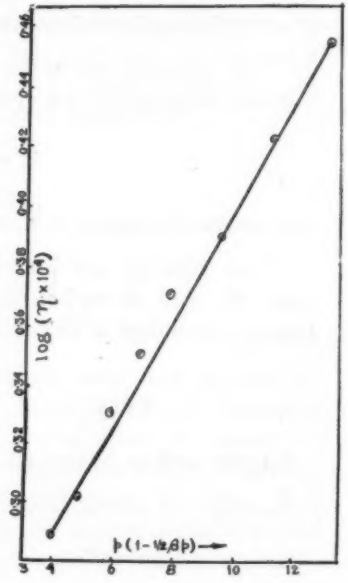

FIG. 2

Thus, the procedure adopted herein and equations (11) and (14), deduced above, not only give a theoretical background for the empirical equation proposed by Boyd and Harkins (equation 1) but also offer a clue to the failure of Joly to arrive at a definite relation between η and p of films formed in aqueous solutions of electrolytes.

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EFFECT OF SNAKE VENOMS ON CO-ENZYME-I

By Kanai Lal Bhattacharya

The effect of the venoms of cobra, banded krait and Russell's viper on the breakdown of co-enzyme-I has been studied. All the three venoms possess strong nucleotidase activity (*i.e* hydrolyse the co-enzyme-I at its phosphate linkage) but this activity is completely lost, on heating for 30 minutes, cobra venom at 65°, banded krait venom at 63°, and Russell's viper venom at 70°. The krait venom can liberate nicotinic acidamide from the co-enzyme-I, but the other two are inactive in this respect. This active principle of the krait venom is also destroyed, when it is heated at 63° for 30 minutes.

Co-enzyme-I is known to play an important part in the breakdown of the tissue metabolites into simpler ones. Hence, to ascertain the precise nature of the inhibition of biological process by the snake venoms, it is essential to study their effect on the co-enzyme-I *in vitro*. Chain (*Biochem. J.*, 1939, **33**, 407) found certain snake venoms to inhibit the anaerobic oxidation of lactic, pyruvic acids, etc., and attributed the inhibition to the hydrolysis of the co-enzyme-I by the venom used, at the phosphate linkage.

Handler and Klien (*J. Biol. Chem.*, 1942, **143**, 49) reported that the inactivation of pyridine nucleotide by animal tissues *in vitro* was casued by the liberation of nicotinic acidamide from the nucleotide molecule. It is therefore worthwhile to investigate whether a snake venom can also breakdown the co-enzyme-I at the nicotinic acidamide linkage. The results of such an investigation are recorded in this paper.

Experimental

Effect of Snake Venom at the Phosphate Linkage of Co-enzyme-I

In order to study the effect of the venoms of cobra, Russell's viper and banded krait on the co-enzyme-I, the free phosphoric acid liberated from the co-enzyme-I by the action of the above venoms was estimated, in the presence of bicarbonate Ringer, by measuring the CO_2 evolved in the Warburg's manometer in the following way.

A solution of a venom (0.5%) was made in bicarbonate Ringer and 0.2 c.c. of the solution was added to latter of *p*H 7.3 contained in the main compartment of the Warburg flasks, while 0.5 c.c. or 1.0 c.c. of the co-enzyme-I in bicarbonate Ringer (4 mg./c.c.) was kept in the side tube of the flask. The total volume in each flask was 3 c.c. The flask was fitted to the manometer and the air was displaced by a mixture of 95% N_2 and 5% CO_2. The entire arrangement was shaken in a thermostat bath at 37° ± 0.1° for 15 minutes. The liquid levels in the manometer tubes were adjusted to the zero reading, the taps were closed and the co-enzyme-I was washed into the main compartment. The rate of breakdown of co-enzyme-I was studied by measuring the CO_2 evolved at intervals of 15 minutes. Some typical results are recorded in Table I.

TABLE I

Co-enzyme used = 0.66 mg./c.c.

Venom. c.c.	CO_2 evolved in mm^3. (calc. at N.T.P.) during 15 min.	30 min.	45 min.	60 min.	75 min.
		Cobra venom.			
0.33 mg.	137	147	147	147	147
		Banded krait venom.			
0.33	87	116	146	174	189
		Russell's viper venom.			
0.33	156	156	156	156	156

The sample of co-enzyme-I always contained the same free phosphoric acid. It was neutralised when the co-enzyme-I was dissolved in bicarbonate Ringer. Some experiments were conducted with aqueous solution of co-enzyme-I and these solutions were acidic in reaction. From the results obtained from these experiments it was found that when 0.33 mg./c.c. of venom was allowed to react with 0.66 mg./ c.c. of co-enzyme-I for 1 hour, 80 mm^3 of CO_2 (mean of 3 experiments) in case of cobra venom, 72mm^3 of CO_2 (mean of 3 experiments) in case of Russell's viper venom and 92mm^3 of CO_2 (mean of 2 experiments) in case of banded krait venom, were envolved.

From the results it appears that all the three venoms possess strong nucleotidase activity although the rate of breakdown of co-enzyme-I by different venoms, is different. The nucleotidase present in the cobra and Russell's viper venom is rapid in its action and within 20 minutes 0.33 mg. of the venoms breakdown 0.66 mg. of co-enzyme-I, whereas the nucleotidase present in the banded krait venom is rather slow in its action compared to the action of nucleotidase present in the cobra venom and Russell's viper venom ; 0.33 mg. of krait venom takes about 1 hour and 15 minutes to breakdown 0.66 mg. of co-enzyme-I.

Effect of Heating on the Nucleotidase Activity of the Venoms

To study the effect of heating on the activity of the nucleotidase present in the snake venoms, 0.5% solutions of the venoms in distilled water were heated at different temperatures for 30 minutes. The solutions were then cooled and used as described before. The results are recorded in Table II.

Table II shows that the nucleotidase activity of cobra venom begins to fall at 60° and is completely lost at 65°, whereas the activity of banded krait venom is completely lost at 63°, the loss of activity starting from 60°. The Russell's viper venom is more heat stable than the venoms of cobra and banded krait, so far as this activity is concerned. Its activity begins to fall at 65° and is completely lost at 70°.

Effect of Snake venoms on the Nicotinic Acidamide Linkage of Co-enzyme-I

To study the effect of snake venoms on the breakdown of co-enzyme-I in nicotinic acidamide linkage, the following procedure was addopted. The solutions of the venoms and co-enzyme-I (1 mg./c.c.) were made separately in phosphate buffer of p_H 7.4 and equal

TABLE II

Venom/c.c. = 0.33 mg. Co enzyme-I/c.c. = 0.66 mg.

Heated at.	Cobra venom. CO_2 evolved. in 90 min.	by venom.	Heated at.	Banded krait venom. CO_2 evolved. in 90 min.	by venom.	Heated at.	Russell's viper venom. CO_2 evolveed. in 90 min.	by venom.
—	100 mm^3.	—	—	101 mm^3.	—	—	108 mm^3	—
Normal	181	81mm^3.	Normal	190	89 mm^3.	Normal	183	75 mm^3
60°	152	52	60°	125	24	60°	185	77
65°	97	Nil	60°	130	29	65°	132	24
—	95	—	63°	100	1	70°	99	Nil
Normal	170	75	63°	97	Nil	—	103	—
60°	140	45				Normal	166	63
65°	97	2				65°	127	24
						70°	98	Nil

TABLE III

Venom/c.c.=0.2 mg. Co-enzyme-I/c.c.=0.2 mg.

Cobra venom. Nictonic acidamide liberated Total.	by the venom	Heat at.	Banded krait venom. Nictonic acidamide liberated Total.	by the venom.	Russell's viper venom. Nicot. amide liberated. Total.	by the venom.
44 μg.	—		27 μg	—	46 μg.	—
33	Nil		130	103 μg.	42	Nil
34	,,	70°	38	11	51	5μg
42	—		39	—		
30	Nil		135	94		
35	,,	65°	37	Nil		
			42	—		
			136	94		
		60°	132	90		
			23	—		
			128	105		
		63°	20	Nil		
			49	—		
			142	93		
		63°	52	3		

volumes of each were mixed together in a test tube, the final volume being made up to 5.0 c.c. with the addition of phosphate buffer of p_H 7.4. Control without venom was also kept, because the sample of co enzyme contained some free nicotinic acidamide. The test tubes were incubated at 37.4° ± 0.1° for 1 hour and the nicotinic acidamide liberated was estimated colorimetrically by a modified method of Wang and Kodicek (*Biochem. J.*, 1943, **37**, 530).

A solution containing 10 g. of aniline in 90 c.c. of ethanol was used as the colouring agent and the colour intensity was matched by using "Lumitron model 402 E". In this method a linear relationship is found to hold good with increasing concentration of nicotinic acidamade, up to 4 g./c.c. Before the estimation was made, it was necessary to ascertain the free nicotinic acid present in the sample of co-enzyme-I, as its presence would influence the results (Wang and Kodicek, *loc. cit.*). So it was estimated according to Chowdhury and Kodicek (*ibid.*, 1949, **44**, 343) and it was found that all the nicotinic acid present in the sample was in the amide form and there was no free nicotinic acid. The results are shown in Table III.

The results recorded aboye show that co-enzyme-I is broken down at the nicotinic acidamide linkage by banded krait venom only and not by cobra and Russell's viper venoms. This activity of the banded krait venom is found to be completely lost when the venom is heated at 63° for 30 minutes.

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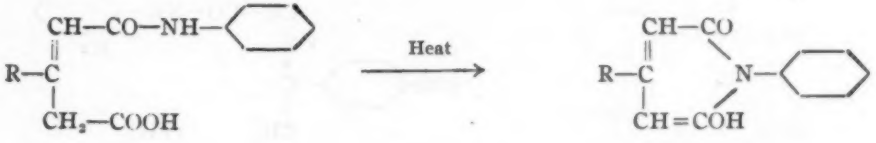
ACTION OF ANILINE AND OTHER PRIMARY AMINES ON THE ANHYDRIDES OF β-ARYLGLUTACONIC ACIDS. PART I. FORMATION AND DECARBOXYLATION OF SEMIANILIDES

By S. S. Karmarkar and V. M. Bhave

Effect of heat and alkali on substituted semianilides and naphthylamides of β-arylglutaconic acids has been studied.

It is well known that the β-arylglutaconic anhydrides react with aniline to give their semianilides. These ordinarily exist in the *cis* form, as they give the corresponding anils on further heating (Thorpe and Bland, *J. Chem. Soc.*, 1912, **101**, 861).



(I) (II, enol form)

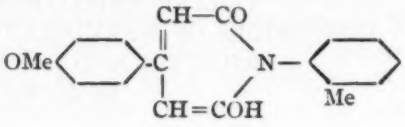
[R = substituted aryl radical].

It has been shown by Bhave and Joshi and Bhave and Nerurkar (*private communication*) that if the aniline portion of the semianilide carries a carbomethoxy substituent in the *ortho* position, then the resulting *o*-carbomethoxysemianilides of β-arylglutaconic acids can be obtained in *cis* and *trans* forms.

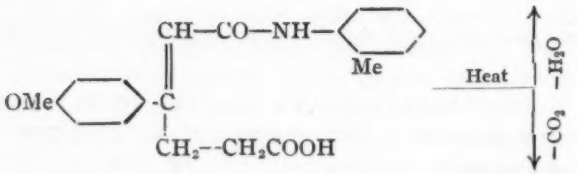
With a view to preparing similar compounds, but containing different substituents in different positions, the present authors have prepared several such compounds. First they prepared, by the action of *o*-methylaniline on β-(4-methoxyphenyl)-glutaconic anhydride, *o*-methylsemianilide of β-(4-methoxyphenyl)-glutaconic acid. This compound was found to exist in the *cis* form, as it readily gave the corresponding anil. When attempts were made to convert this *cis* form into its *trans* form by Joshi, Nerurkar and Bhave's modification of Thorpe's method (*J. Chem. Soc.*, 1912, **101**, 864; 1911, **99**, 2214), contrary to the expectation, no *cis* to *trans* change could be effected. Therefore the effect of heat on the above semianilide was studied more critically.

It was found that when the above semianilide was heated at a higher temperature *i.e.*, at its melting point, it decomposed. The gases given out were found to consist of CO_2 and water. It is well known that usually the semianilides on heating lose a molecule of water to give their anils (enol form). The appearance of CO_2 in the above experiment was therefore unexpected. The resulting mass on fractional crystallisation gave two distinct substances: (1) m.p. 158° was found to be the expected anil (enol form), but in addition another neutral substance (2) m.p. 163° was found to accom-

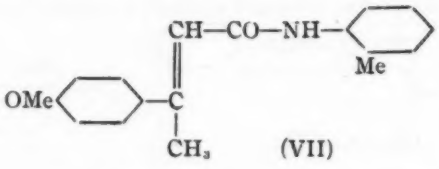
pany the anil. The second substance was found to differ from the corresponding semianilide by a molecule of CO_2. This clearly shows that in the above treatment a part of the semianilide suffers dehydration giving the anil of m.p. 158°, while a part suffers decarboxylation giving rise to the neutral substance of m. p. 163°.



(VI)



(V)

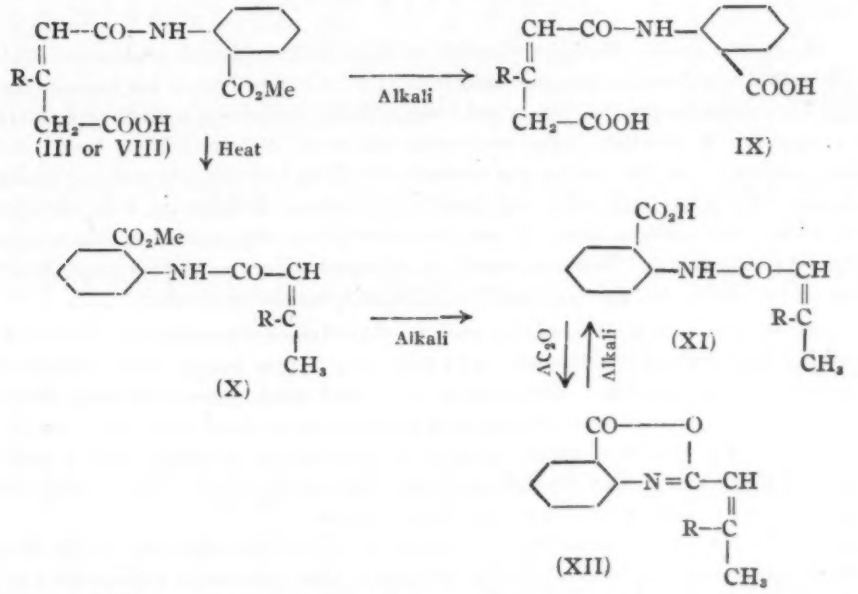


(VII)

This has been found to be a general property of the semianilides of β-arylglutaconic acids, since on trying the reaction on the substituted semianilides and naphthylamides of β-arylglutaconic acids obtained by the action of *m*-methylaniline, *p*-methylaniline, *m*-nitroaniline, *o*-methoxyaniline, *p*-methoxyaniline, *p*-carbomethoxyaniline, α-naphthylamine, β-naphthylamine with β-(4-methoxyphenyl)-glutaconic anhydride and *o*-carbomethoxyaniline with β-(2-methyl-4 methoxy-5-*iso*propylphenyl)-glutaconic anhydride, similar results have been obtained. However, semianilides containing nitro substituents in *o*- and *p*-positions, viz., *o*-and *p*- nitrosemianilides of β-(4-methoxyphenyl)-glutaconic acid, could not be prepared by any of the usual methods.

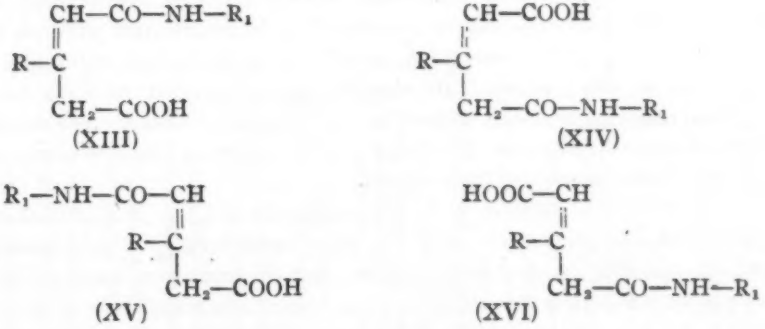
In view of the above observations regarding decarboxylation, other previously known semianilides of β-(4-methoxyphenyl)-glutaconic acid, viz., *o*-carbomethoxysemianilide (*loc. cit.*) and unsubstituted semianilide were subjected to similar heat treatment and they were found to behave similarly.

Incidentally it has been found that the *p*-carbomethoxysemianilide of β-(4-methoxyphenyl)-glutaconic acid (22), and *o*-carbomethoxysemianilide of β-(2-methyl-4-methoxy-5-*iso*propylphenyl)-glutaconic acid (27) get hydrolysed to the corresponding carboxy-acids (23 and 28 respectively). So also the decarboxylation products (19, 24 and 29), obtained by the method described in Expt. No. 3 from the respective β-aryiglutaconic anhydride and the respective substituted aniline, were hydrolysed to the corresponding carboxy-acids (20, 25 and 30 respectively). These acids (20 and 30) were found to be converted further into the lactone type of compounds (21 and 31) by the action of acetic anhydride and could be hydrolysed back to the original acids by the action of alkali, as will be seen from the following scheme:



[where R = β-(4-methoxyphenyl) and β-(2-methyl-4 methoxy-5 *iso*propylphenyl) radical].

It will be seen from the study of the above compounds that at this stage it is not possible to state the exact structure of the decarboxylation products, because in spite of several semianilides of β-arylglutaconic acids being known, still (*i*) the position of the aniline in the semianilide has not been proved unambiguously in their cases and therefore according to the position of the double bond, the compounds can possess either of the following two alternative structures:



(where R and R_1 are phenyl radicals).

and (*ii*) each of these (XIII) and (XIV) can again exist in *cis* and *trans* forms and the decarboxylation products from these various forms will have different structures.

The results of the further study on these points will be communicated in due course.

EXPERIMENTAL

Expt. No. 1. cis-o-*Methylsemianilide of β-(4-Methoxyphenyl)-glutaconic Acid* (V).—β-(4-Methoxyphenyl)-glutaconic anhydride (1 g.) was dissolved in hot benzene (40 c.c.) and to it *o*-methylaniline (0.49 g., 1 mol.) was added, when after a short time, a solid began to separate. It was then heated on a water-bath at 60°-65° for half an hour. Benzene was removed and the residue was washed with dilute hydrochloric acid and finally with water. This impure grey solid was dissolved in sodium bicarbonate and reprecipitated by dilute hydrochloric acid. It was crystallised from ethyl alcohol in colorless needles, m.p. 174° (decomp.). This compound, when heated above its melting point, gave partly the corresponding hydroxy-anil and partly its decarboxylation product.

Expt. No. 2. o-*Methylhydroxy-anil of β-(4-Methoxyphenyl)-glutaconic Acid* (VI).—β-(4-Methoxyphenyl)-glutaconic anhydride (1 g.) was boiled with *o*-methylaniline (2 c.c.) for 10 minutes. The viscous liquid on cooling formed a resinous mass which was thoroughly washed with concentrated hydrochloric acid and then with water. The resulting mass was then extracted with 2*N*-NaOH and acidified when a grey solid was obtained which was crystallised from ethyl alcohol, m.p. 158°. The alcoholic solution gave a light brown colour with ferric chloride.

Expt. No. 3. *Decarboxylation Product of* o-*Methylsemianilide of β-(4-Methoxyphenyl)-glutaconic Acid* (VII).—This substance was obtained as a by-product in Expt. No. 2. After the sodium hydroxide extraction, this substance remained insoluble in sodium hydroxide. It was crystallised from dilute acetic acid or dilute ethyl alcohol in pinkish plates, m.p. 163°, yield 0.3 g.

Expt. No. 4. m-*Nitrohydroxy-anil and the corresponding Decarboxylation Product of β-(4-Methoxyphenyl)-glutaconic Acid.*—While preparing this compound the procedure was slightly modified. *m*-Nitroaniline (2 g.) was melted in a r. b. flask (25 c.c.) and β-(4 methoxyphenyl)-glutaconic anhydride (1 g.) was added. The resulting mass was heated for 10 minutes and cooled. The rest of the procedure was similar to Expt. No.2. The alkali-soluble product was the required hydroxy-anil, m.p. 246-47° and the insoluble substance was the corresponding decarboxylation product, m.p. 143°.

Expt. No. 5. cis-*β-Seminaphthylamide of β-(4 Methoxyphenyl)-glutaconic Acid.*—This compound was prepared in the same manner as described in Expt No. 1 from β-(4-methoxyphenyl)-glutaconic anhydride and β-naphthylamine. The peculiar property of this substance is that when it is boiled with glacial acetic acid it is converted quantitatively into the corresponding hydroxy-anil, m.p. 265°.

Expt. No. 6. *Hydrolysis of* o-*Carbomethoxysemianilide of β-(2-Methyl-4-methoxy-5-isopropylphenyl)-glutaconic Acid to the corresponding Carboxy-acid.*—*o*-Carbomethoxysemianilide of β-(2-methyl-4-methoxy-5-*iso*propylphenyl)-glutaconic acid (1 g.) (obtained by the method described in Expt. No.1) was dissolved in alcohol (15 c.c.) and NaOH (2 c.c. 12.5 *N*) was added. It was kept for 12 hours at room temperature. Alcohol was evaporated off and the residue was dissolved in water (25 c.c.). It was filtered and acidified. It was purified by dissolving in sodium bicarbonate solution and precipitating it by dilute HCl and then crystallised from ethyl alcohol in small needles, m.p. 171° (decomp.), yield 0.6 g.

TABLE I

G stands for β-(4-methoxyphenyl)-glutaconic acid.

	Compounds.	Formula.	M. p	% Carbon.		% Hydrogen.		Equivalent.	
				Found.	Calc.	Found.	Calc.	Found.	Calc.
1.	*'Cis'* o-methylsemianilide of G	$C_{19}H_{19}O_4N$	174°(decomp)	70.21	70.15	5.80	5.84	324.8	325.0
2.	Anil of (1)	$C_{19}H_{17}O_3N$	158°	74.49	74.27	5.98	5.53	305.9	307.0
3.	*'Trans'* decarboxylation product of (1)	$C_{18}H_{19}O_2N$	163°	76.72	76.88	6.91	6.76	—	—
4.	*'Cis'* m-methylsemianilide of G	$C_{19}H_{19}O_4N$	173°(decomp)	70.11	70.15	6.02	5.84	322.8	325.0
5.	Anil of (4)	$C_{19}H_{17}O_3N$	193°	73.99	74.27	5.68	5.53	306.3	307.0
6.	*'Trans'* decarboxylation product of (4)	$C_{18}H_{19}O_2N$	145°	76.88	76.88	6.81	6.76	—	—
7.	*'Cis'* p-methylsemianilide of G	$C_{19}H_{19}O_4N$	175°(decomp.)	70.20	70.15	5.39	5.84	325.3	325.0
8.	Anil of (7)	$C_{19}H_{17}O_3N$	204°	74.49	74.27	5.86	5.53	306.6	307.0
9	*'Trans'* decarboxylation product of (7)	$C_{18}H_{19}O_2N$	124°	76.43	76.88	6.57	6.76	—	—
10.	*'Cis'* m-nitrosemianilide of G	$C_{18}H_{16}O_6N_2$	195°(decomp.)	60.23	60.68	4.04	4.49	352.9	356.0
11.	Anil of (10)	$C_{18}H_{14}O_5N_2$	246-47°	63.90	63.92	4.44	4.14	337.4	338.0
12.	*'Trans'* decarboxylation product of (10)	$C_{17}H_{16}O_4N_2$	143°	65.03	65.37	5.43	5.13	—	—
13.	*'Cis'* o-methoxysemianilide of G	$C_{19}H_{19}O_5N$	171°(decomp.)	—	—	—	—	343.7	341.0
14.	Anil of (13)	$C_{19}H_{17}O_4N$	188-89°	—	—	—	—	323.6	323.0
15.	*'Trans'* decarboxylation product of (13)	$C_{18}H_{19}O_3N$	88°	72.31	72.73	6.28	6.39	—	—
16.	*'Cis'* p-methoxysemianilide of G	$C_{19}H_{19}O_5N$	181°(decomp)	67.02	66.85	5.70	5.57	341.4	341.0
17.	Anil of (16)	$C_{19}H_{17}O_4N$	201-202°	70.30	70.58	5.02	5.26	321.6	323.0
18.	*'Trans'* decarboxylation product of (16)	$C_{18}H_{19}O_3N$	144°	72.57	72.71	6.34	6.39	—	—
19.	*'Trans'* decarboxylation product of the o-carbomethoxysemianilide of G	$C_{19}H_{19}O_4N$	101°	70.33	70.15	5.93	5.84	—	—
20.	Hydrolysis product of (19)	$C_{18}H_{17}O_4N$	164-65°	—	—	—	—	311.7	311.0
21.	Lactone of (20).	$C_{18}H_{15}O_3N$	79°	73.87	73.72	5.08	5.11	—	—
22.	*'Cis'* p-carbomethoxysemianilide of G	$C_{20}H_{19}O_6N$	181°(decomp.)	65.25	65.04	5.22	5.15	370.1	369.0
23.	Hydrolysis product of (22).	$C_{19}H_{17}O_6N$	216-17°	64.19	64.22	4.67	4.78	177.7	177.5
24.	*'Trans'* decarboxylation product of (22)	$C_{19}H_{19}O_4N$	148-49°	69.92	70.15	5.71	5.84	—	—
25.	Hydrolysis product of (24).	$C_{18}H_{17}O_4N$	247°(decomp.)	—	—	—	—	310.9	311.0
26.	*'Trans'* decarboxylation product of the semianilide of G	$C_{17}H_{17}O_2N$	144°	76.38	76.40	6.19	6.36	—	—
27.	*'Cis'* o-carbomethoxysemianilide of β-(2-methyl-4-methoxy-5-*iso*propylphenyl)-glutaconic acid	$C_{24}H_{27}O_6N$	136°	67.50	67.76	6.24	6.35	424.3	425.0
28.	Hydrolysis product of (27).	$C_{23}H_{25}O_6N$	171°(decomp.)	67.28	67.16	6.22	6.08	206.4	205.5
29.	*'Trans'* decarboxylation product of (27)	$C_{23}H_{27}O_4N$	83°	72.23	72.44	7.07	7.08	—	—
30.	Hydrolysis product of (29)	$C_{22}H_{25}O_4N$	136-37°	72.40	71.93	6.91	6.81	366.8	367.0
31.	Lactone of (30)	$C_{22}H_{23}O_3N$	91-92°	75.61	75.65	6.36	6.59	—	—
32.	*'Cis'* seminaphthylamide of G	$C_{23}H_{19}O_4N$	188°(decomp.)	73.60	73.13	5.68	5.26	361.4	361.0
33.	Anil of (32)	$C_{22}H_{17}O_3N$	227-28°	77.18	76.96	5.39	4.95	341.0	343.0
34.	*'Trans'* decarboxylation product of (32)	$C_{21}H_{19}O_2N$	158°	79.29	79.49	5.83	5.99	—	—
35.	*'Cis'* seminaphthylamide of G	$C_{22}H_{19}O_4N$	198°(decomp.)	73.30	73.13	5.11	5.26	361.8	361.0
36.	Anil of (35)	$C_{29}H_{17}O_3N$	265°	76.43	76.93	4.30	4.95	343.6	343.0
37.	*'Trans'* decarboxylation product of (35)	$C_{21}H_{19}O_2N$	180-81°	79.18	79.49	6.29	5.99	—	

Compound No. 25 was prepared in the same way and described in this experiment.

Expt. No. 7. Hydrolysis of the Decarboxylation Product of o-Carbomethoxysemianilide of β-(2-Methyl-4-methoxy-5-isopropylphenyl)-glutaconic acid was also carried out in the same manner as described in Expt. No. 4, and the corresponding carboxy-acid (m.p. 136-37°) obtained was crystallised from dilute alcohol in small colorless crystals. It is soluble in ethyl alcohol, ether and acetic acid.

Compounds No. 20 and 25 were also prepared in the same manner as described in this experiment.

Expt. No. 8. Lactone of the above Acid of m.p. 136-37°.—The acid of m.p. 136-37° (mentioned in Expt No. 5) (1 g.) was heated with acetic anhydride (6 c.c.) on a boiling water-bath for 1 hour, The substance gradually went in soiution with a yellowish colour. The solution was then poured in water (25 c. c.). A yellowish coloured substance in semi-solid state was found to separate. This substance on successive treatment with bicarbonate solution, water and methyl alcohol gave a pale yellow solid. It was crystallised from ethyl alcohol in long colorless needles, m.p. 91-92°.

This substance could be hydrolysed back to the original acid by the action of alkali.

Compound No. 21 was prepared in the same manner as described in this experiment.

By following a similar procedure, as described in experiment Nos. 1 to 8, a number of substituted semianilides, the corresponding anils (enolic form) and the corresponding decarboxylation products have been obtained by the action of substituted primary amines on β-arylglutaconic anhydrides. The different compounds obtained are listed in Table I.

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CHEMISTRY OF ALIPHATIC THIOCARBAMIDES. PART II. N:N-DIMETHYLTHIOCARBAMIDE

By Ranbir Singh and Tilak Chandra Saikia

Chemistry of N:N-dimethylthiocarbamide has been investigated with respect to its formation and interaction with acids, alkalies, nitrous acid, silver nitrate, lead acetate, acetic anhydride and benzyl chloride etc.

Formation of N:N-dimethylthiocarbamide by the isomerisation of dimethylamine thiocyanate at 130° and 150° was reported by Salkowski (*Ber.*, 1893, **26**, 2497, 2505). A 14-17% conversion into the thiocarbamide was achieved but the compound could not be isolated from the mixture. We have prepared the compound therefore by the procedure of Wallach (*Ber.*, 1890, **32**, 1874) by the condensation of dimethylcyanamide with hydrogen sulphide.

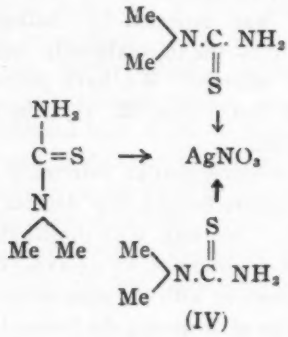
A reinvestigation of the isomeric change, referred to above, was also carried out at 130° and 165°, the latter temperature being a few degrees above the melting point of dimethylthiocarbamide. At 130°, starting with dimethylamine thiocyanate, equilibrium appears to be established within 60 minutes at 14-15% conversion into thiocarbamide (Table I, A); this is in close agreement with the observation of Salkowski (*loc. cit.*). At 165°, the experimental difficulties of observing the forward and back reaction are, indeed, very considerable and besides the isomeric change, there are side reactions and loss of reactants or their derivatives through volatilization. At 165°, within half an hour 13% conversion to thiocarbamide took place. The reaction for longer durations (up to 6 hours) exhibited large variations due to secondary changes and loss of volatile matters (vide Table I, B). The same holds true of the reverse change. The reaction is most probably, a normal reversible change as in the case of thiocarbamide but is vitiated by secondary changes. The reaction is likely to be more amenable to investigation in aqueous solutions or in suitable solvents.

Action of Alkali and Acid.—Like methylthiocarbamide (Sahasrabudhey and Singh, this *Journal*, 1953, **30**, 499) and this semicarbazide (*ibid.*, 1941, **18**, 225) but in contrast with phenylthiocarbamide (*ibid.*, 1935, **12**, 635 *et seq*) and thiocarbanilide, N:N-dimethylthiocarbamide is more stable towards boiling acid solutions than to alkalies. No perceptible decomposition was observed even after an hour's boiling with *N*- or 5*N*-H_2SO_4. With *N* and 5*N* boiling NaOH it decomposed into 28.9% and 41.1% dimethylamine and 6% and 57.7% H_2S respectively. The total absence of thiocyanic acid in the decomposition products is indeed notable. This fact suggests that in boiling solutions N:N-dimethylthiocarbamide does not revert back to dimethylamine thiocyanate.

Desulphurisation.—It has been reported that unlike monoalkyl- and mono- and diaryl-thiocarbamides, dialkylthiocarbamides cannot be desulphurised by alkaline lead acetate or mercuric oxide (Dixon, *J. Chem. Soc.*, 1893, **63**, 318; Sahasrabudhey and Krall, this *Journal*, 1944, **21**, 63). Our experiments indicate that as far as mono- and

disubstituted derivatives are concerned, this difference is rather of degree than of kind (vide Experimental), the underlying reaction in both cases being the elimination of the elements of hydrogen sulphide and formation of the corresponding cyanamide. The trialkyl and tetraalkyl derivatives, as indeed is expected on this view, have been found absolutely non-desulphurisable under these conditions.

Reaction with Silver Nitrate.—Like other thiocarbamides (Rathke, *Ber.*, 1881, **14**, 1774; Lal and Krall, this *Journal*, 1937, **14**, 474; Sahasrabudhey and Singh, *loc. cit.*) N:N-dimethylthiocarbamide also forms complexes (I to IV) with silver nitrate which vary in composition depending on conditions of formation, viz., temperature and relative concentration of the reactants. Structures of the complexes (I) and (II) (III) are analogous to the corresponding complexes of methylthiocarbamides (vide this *Journal*, 1953, **30**, 500).



(IV)

At ordinary temperature with excess of silver nitrate (I) or mixtures of (I) and (II) result, while with excess of the thiocarbamide, (III) and (IV) are formed. In boiling solutions even with excess of thiocarbamide only (I) and (II) or their mixtures could be obtained. No complex compound separates when either the thiocarbamide or silver nitrate is in overwhelming excess. The complexes are stable only in presence of a little dilute nitric acid, otherwise decomposition (desulphurisation) sets in (vide Table III).

Action of Nitrous Acid and Oxidation.—As is expected on analogy with other thiocarbamides (Werner, *J. Chem. Soc.*, 1912, **101**, 2180; this *Journal*, 1935, **12**, 640; 1951, **28**, 119) nitrous acid reacts with N:N-dimethylthiocarbamide in two ways, depending on the acidity of the medium.

(*i*) *In a weak acid medium* (*dilute acetic acid*):

$$Me_2.N.CS.\ NH_2 \xrightarrow{HNO_2} Me_2.N\text{-}\underset{\underset{S}{\|}}{C}\text{-}OH + N_2 + H_2O$$

(*ii*) *In a strong acid medium* (*dilute sulphuric acid*):

$$Me_2.N.CS.\ NH_2 \xrightarrow[HX]{HNO_2} [Me_2.N.CS.\ NH_2]X + H_2O + NO$$

(V)

The reaction (*i*) is much slower in the present case as compared with thiocarbamide and N-methylthiocarbamide. The oxidation product (V) obtained in (*ii*) belongs to the

class of the so-called "formamidine disulphide salts". It was examined separately (this *Journal*, 1952, **29**, 636).

Reaction with acetic anhydride in the usual way afforded an acetyl derivative:

$$Me_2N.CS.NHCOCH_3.$$

EXPERIMENTAL

Isomeric Change of Dimethylamine Thiocyanate to Dimethylthiocarbamide and vice versa

Dimethylamine thiocyanate was prepared by passing dimethylamine, obtained from *p*-nitrosodimethylaniline or tetramethylthiuram disulphide (this *Journal*, 1952, **29**, 489) through an ethereal solution of thiocyanic acid obtained by the action of hydrogen sulphide on lead thiocyanate. Its purity was confirmed by estimating the amine and thiocyanate content.

N:N-Dimethylthiocarbamide was prepared by Wallach's method (*loc.cit.*). After repeated crystallisations and decolorisation by animal charcoal a colorless pure sample, m.p. 161°, was obtained.

The procedure followed for studying the isomeric change was the same as described in Part I with methylthiocarbamide (Sahasrabudhey and Singh, *loc. cit.*); about 0.2 g. of the substance was taken in each of twelve test tubes. Experiments were carried out both with dimethylamine thiocyanate and N:N-dimethylthiocarbamide at 130° and 165°. In independent experiments losses (*i*) in weight of the test tube contents on heating and (*ii*) in thiocyanate + thiocarbamide content, as measured by mercuric nitrate titre value, were estimated. The results are presented in Tables I-II.

Hydrolytic decomposition was effected with 1.04 g. of dimethylthiocarbamide in a similar way as described in Part I (*loc. cit.*). In acid hydrolysis (*N*- or 5*N*-H_2SO_4) no other product excepting the unchanged thiocarbamide could be detected. In the case of alkali hydrolysis (*N*-or 5*N*-NaOH) the hydrolytic liquor was found to contain H_2S and dimethylamine was detected in the wash-trap. The amount of amine was found out by difference by estimating the acid in the trap; H_2S was estimated iodimetrically. With normal alkali, amine 28.9% and H_2S 6% and with 5*N* alkali, amine 41.1% and H_2S 57.7%, calculated on the basis of total decomposition, were found.

Desulphurisation.—To dimethylthiocarbamide (0.26 g.), dissolved in water (150 c.c.), were added NaOH (1g.) and cadmium sulphate (1·2 g.). At 30° no desulphurisation took place even after 24 hours, but on an hour's boiling almost complete desulphurisation to cyanamide was observed as indicated by titration with mercuric nitrate (this Journal, 1953, **30**, 223). Under comparable conditions thiocarbamide and methylthiocarbamide are desulphurised with greater ease.

In boiling benzene and alcohol, desulphurisation was studied with copper powder which formed copper sulphide; the estimation of sulphur from the latter by usual methods indicated the extent of desulphurisation. Desulphurisation was observed in absolute alcohol and benzene to the extent of 20% and 28% respectively. The influence of medium on desulphurisation is suggestive.

TABLE I

Isomerisation of dimethylamine thiocyanate to dimethylthiocarbamide.

Expt. No.	Duration of heating.	Mercuric nitrate titre value. Without desulphurisation.	After desulphurisation.	% Loss in thiocyanate content.	% Isomerisation. Apparent (calc. on the initial conc. of thiocyanate, 19.3 c.c.).	Corr. for loss calc. from columns 3. and 4).
			A. At 130°.			
1	0.0 min.	19.3 c.c.	19.30 c.c.	0.0	0.0	0.0
2	10		19.05	Not perceptible	1.29	1.29
3	20		18.70	,,	3.10	3.10
4	30		18.35	,,	4 92	4.92
5	40		17.85	,,	7.51	7.51
6	50		17.05	,,	11.68	11.68
7	60	19.0	16.35	1.54	15.80	13.94
8	2 hrs.	18.8	15.9	2.59	17.62	15.4
9	3	18.6	15.8	3.63	18.13	15.0
10	4	18.5	16.0	4.14	17.09	13.5
11	5	18.5	15.75	4.14	18.40	14.9
12	6	18.4	15.70	4.66	18.66	14.7
			B. At 165°.			
1	0.0 min.	21.85 c.c.	21.85 c.c.			—
2	10		19.60			10.30
3	20		19.35			11.44
4	30		19.10			12.57
5	40		19.10			12.57
6	50		19.00			13.04
7	60	21.3	18.55	2.52	15.10	12.91
8	90	...	17.85	...	18.30	16.19
9	2 hrs.	21.05	17.5	3.66	19 90	16.86
10	3	20.8	17.0	4.80	22.20	18.26
11	4	20.7	16.4	5.27	24.94	20.77
12	5	20.45	16.1	6.40	26.31	21.27
13	6	20.20	15.8	7 55	27.68	21.78

N. B. The figures in columns 3 to 7 clearly indicate the interference due to the loss in volatile matter (not measured) and that in thiocyanate content (column 5). The isomerisation figures in column 7 have been corrected for loss in thiocyanate but are subject to an uncertain reduction due to loss of thiocyanate in other ways. But they adequately represent a tendency towards equilibrium.

TABLE II

*Isomerisation of N:N-dimethylthiocarbamide to dimethyl thiocyanate at 165° and 130° *.*

Expt. No.	Dnration of heating.	Mercuric nitrate titre value. Without desulphurisation.	After desulphurisation.	% Loss in thiocyanate.	Wt.	% Isomerisation. Apparent.	Corrected for loss.
1	0.0 min.	17.55 c.c.					
2	10		15.90 c.c.			90.6 **	90.6
3	20		15.70			89.4	89.4
4	30		15.40			87.7	87.7
5	40		15.35			87.5	87.5
6	50		15.00			86.4	85.4
7	60	17.2	14.55	1.99	0.6	82.7	84.5
8	2 hrs.	15.9	14.40	9.40	3.5	81 8	90.5
9	3	15.2	14.10	13.40	7.3	80.4	92.7
10	4	14.4	13.80	17.95	11.7	78.6	95.8
11	5	14.1	12.30	19.66	15.0	69.9	87.2
12	6	14.0	11.90	20.23	16.1	67.8	85.0

*At 130° it was observed that even in 75 min. equilibrium had not been reached ; 2.8, 5.1, 17.6, 28.5, 29.6, 40.4 and 62.7% conversion had taken place in 10, 20, 30, 40, 50, 60 and 75 min. respectively.

** Note the very considerable complementary agreement in figures in columns 7 and 8 of this table and those in the corrosponding columns of Table IB (at 165°).

TABLE III

Complexes of silver nitrate with N: N-dimethylthiocarbamide.

No.	$AgNO_3$: thiocyanate.	$AgNO_3$ taken (in 10% soln.).	Thiocarb. taken (10% soln.).	Wt. of Ag salt ignited.	Wt. of Ag recovered.	Ratios of Ag and loss. Found.	Calc.	Composition corresponding to column 8.
1	1:1	1.70 g.	1.04 g.	0.4802	0.2118 g.	432:559.2	432:560	$2[Thi.,AgNO_3]+Thi.,2AgNO_3$
2	2:1	3.40	1.04	0.4414	0.1990	324:394.8	324:394	$Thi.,AgNO_3+Thi.,2AgNO_3$
3	4:1	6.40	1.04	0.5304	0.2526	216:237.6	216:228	$Thi.,2AgNO_3$
4	1:2	0.85	1.04	(i)0.3764	0.1130	108:251.7	108:270	$2Thi.,AgNO_3$
	,,	,,	,,	(ii)0.2204	0.0660	108:252.8	,, ,,	Do
5	1:4	0.85	2.08	(i)0.5244	0.1222	108:369.2	108:374	$3Thi.,AgNO_3$
	,,	,,	,,	(ii)0.3400	0.0800	108:351.0		Do
6	1:8	0.42	,,	No ppt.	...	...	...	
7	8:1	6.80	0.52	No ppt.	...	...	...	
8	1:1	1.70	1.04	(i)0.5246	0.2304	432:552.0	432:560	$2[Thi.,AgNO_3]+Thi.,2AgNO_3$
9	,,	,,	,,	0.4966	0.2270	324:384.6	324:394	$Thi.,AgNO_3+Thi.,2AgNO_3$
10	2:1	3.40	,,	(i)0.5608	0.2684	216:235.2	216:228	$Thi.,2AgNO_3$
				(ii)0.5744	0.2758	216:233.8	216:228	Do
			,,	(i)0.4322	0.1990	324:379.5	324:394	$Thi.,AgNO_3+Thi.,2AgNO_3$
				(ii)0.3168	0.1428	324:394.8	324:394	Do Do

Expt. Nos. 1-7 conducted in cold and the rest in boiling soln.

Loss in wt. calculated from the difference in wt. of Ag salt ignited and wt. of Ag recovered.

Interaction with Nitrous Acid.—The reaction was studied following the technique of Werner (*J. Chem. Soc.*, 1912, **101**, 2180) and Krall (this *Journal*, 1935, **12**, 640; 1937, **14**, 478; 1938, **15**, 217) in a Lunge's nitrometer with mg. molar quantities of reactants, viz. 0.104 g. dimethylthiocarbamide and one or two equivalents of sodium nitrite in a normal acetic acid or sulphuric acid medium. The gas was analysed with ferrous sulphate for nitric oxide and nitrogen and with alcoholic potash for the carbon oxysulphide (this *Journal*, 1952, **29**, 636).

In 1:1 ratio of reactant in a normal acetic acid medium 24.5 c.c. (corrected to N.T.P.) gas were evolved within 30-60 minutes; out of this 55-60% (13.5 to 14.0 c.c.) were nitrogen and 25-30%, nitric oxide and 17-20%, cabon oxysulphide. On addition of a second equivalent of nitrous acid after the completion of the first (1:1 reaction) phase, another .25 c.c. of gas were evolved out of which 6-7 c.c. were nitrogen.

In a normal sulphuric acid medium about 22 c.c. gas (corrected to N.T.P.) were evolved out of which only 1.2 c.c. was nitrogen and rest, nitric oxide. The reaction under this condition therefore is not between $-NH_2$ group and nitrous acid but consists in the oxidation of N:N-dimethylthiocarbamide to the corresponding "formamidine disulphide salt" (cf. Werner, *loc. cit.* this *Journal*, 1952, **29**, 636).

Interaction with Silver Nitrate.—The interaction between N:N-dimethylthiocarbamide and silver nitrate was investigated at room temperature and in boiling solutions with varying proportions of the reactants. The medium was always acidified with a few c.c. of dilute nitric acid otherwise desulphurisation of the thiocarbamide set in. No free acid was liberated from the reactants. The composition of the complexes was determined by estimating silver. The results are presented in Table III.

Interaction with Acetic Anhydride.—Dimethylthiocabamide (2 g.) and acetic anhydride (4 c.c.) with a small quantity of anhydrous zinc chloride were heated for about 5-10 minutes. The mass was poured in water; after sometime a crystalline white substance separated; crystals from alcohol m.p. 212°. (Found : N, 19.0; S, 22.0. Calc. N, 19.18; S, and 21.9 per cent).

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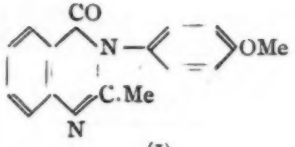
ANTIMALARIALS IN QUINAZOLINE SERIES. PART III

By Megh Kumar Jain and K. S. Narang

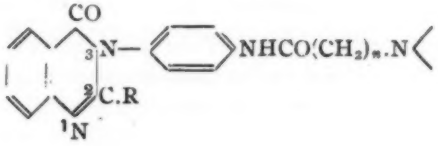
Some 2- and 3- substituted 4-quinazolones have been prepared with a view to testing their antimalarial properties.

Since 2-methyl-3-(*p*-methoxyphenyl)-quinazolone-4 (I) (Miss Shakti Rani, Vig, Gupta and Narang, this *Journal*, 1953, **33**, 332) had been found to be as active as quinine in the preliminary tests against *P. gallinaceum* in chicks, it was considered desirable to further extend the work.



(I)

The present communication records the synthesis of the compounds of the type (II)

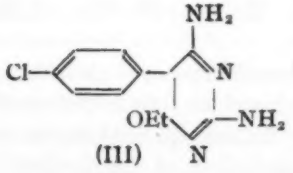


(II, where R = H or Me; $n = 1$ or 2).

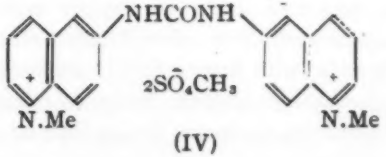
In this series, *p*-aminophenyl group at position 3 has been introduced mainly for the following reasons:—

The amino group is a *para*-directing group like the methoxy group in (I) and in addition it offers certain distinct advantages over the methoxy group in that it enables further introduction of anchoring and basic side chains, so essential in all the antimalarials.

It is significant to note that Daraprim (III) (Falco *et al.*, *Brit. J. Pharmacol.*, 1951, **6**, 185), the most recent and at the same time very promising antimalarial, has an amino group at *para* position to the hetero N, as is the case in the compounds of the present series.



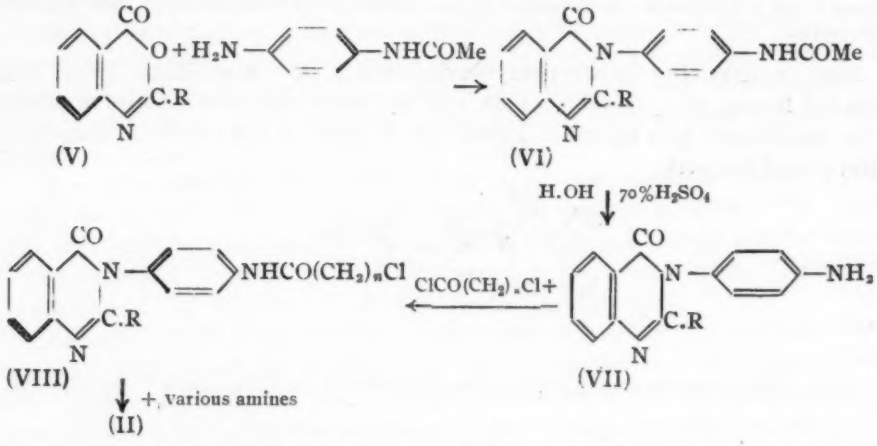
(III)



(IV)

Moreover, Acaprin (IV), the important antiprotozoal drug against Babesiasis, possesses amino groups in the *para* position to the hetero N-atom, and it is quite probable that the compounds of the present series may, in addition to having antimalarial properties, also show activity against other protozoal infections.

The general scheme of the synthesis in the present series can be graphically represented as follows:



It may be noted here that the formation of the 4-quinazolone from the 3:1:4-benzoxazone in each case is an one-step process and not a two-step process as found by Zentmeyer and Wagner (*J. Org. Chem.*, 1949, **14**, 967).

EXPERIMENTAL *

3-(p-*Acetylaminophenyl*)-*quinazolone*-4.—*p*-Aminoacetanilide (4.5 g.) was added to 3:1:4-benzoxazone, prepared from N-formylanthranilic acid (8.2 g.) (Zentmeyer and Wagner, *loc. cit.*), and the mixture was heated on a steam-bath for 5 hours. The resulting yellow mass on crystallisation from glacial acetic acid-ethyl acetate mixture (60% and 40%) gave needles of the base, yield 6.0 g., m.p. 226°. (Found : N, 14.60. $C_{16}H_{13}O_2N_3$ requires N, 15.05 per cent).

3-(p-*Aminophenyl*)-*quinazolone*-4.— 3-(*p*-Acetylaminophenyl)-quinazolone-4 (5 g.) was heated with 70% sulphuric acid (25 c.c.) for 20 minutes. The resulting solution, on cooling, was basified with sodium carbonate solution. The solid so obtained was filtered, washed free of alkali and dried. It was crystallised from alcohol in white fluffy plates, yield 3.5 g., m.p. 180°. (Found: C, 70.73; H, 4.66; N, 18.0. $C_{14}H_{11}ON_3$ requires C, 70.89; H, 4.64; N, 17.72 per cent).

3-(p-*Chloroacetylaminophenyl*)-*quinazolone*-4.—Monochloroacetyl chloride (1 c.c.) was slowly added with stirring to 3-(*p*-aminophenyl)-quinazolone-4(1 g.), moistened with a few drops of dry benzene, during 15 minutes. At the end, the mixture was warmed on a water-bath for 5 minutes (longer heating caused darkening of the product). The

* Mircro-analyses are by Drs. Weiler and Strauss, Oxford.

reaction mixture was basified with sodium bicarbonate solution in the cold. The product was filtered, washed and dried and crystallised from ethyl alcohol in glistening white plates, yield 0.8 g., m.p. 230°(decomp.). (Found: N, 13.60. $C_{16}H_{12}O_2N_3Cl$ requires N, 13.39 per cent).

3-(p-*β-Chloropropionylaminophenyl*)-*quinazolone*-4.—To 3-(*p*-aminophenyl)-quinazolone-4(0.5 g.), moistened with a few drops of dry benzene, was added slowly with stirring *β*-chloropropionyl chloride (0.5 c.c.) during 10 minutes. The resulting mixture was heated on a water-bath for 10 minutes and worked up in the same way as in the case of 3-(*p*-chloroacetylaminophenyl)-quinazolone-4. The base crystallised from ethyl alcohol in glistening white plates, yield 0.6 g., m.p. 245°. (Found : N, 12.49. $C_{17}H_{14}O_2N_3Cl$ requires N, 12.82 per cent).

2-*Methyl*-3-(p-*acetylaminophenyl*)-*quinazolone*-4.—A mixture of *p*-aminoacetanilide (7 g.) and 2-methyl-3:1:4-benzoxazone (7.5 g.) was heated at 130°-140° for 3 hours. The product crystallised from 70% ethyl alcohol in glistening white plates, yield 8.0 g., m.p. 260°. (Found: C, 69.43; H, 5.12; N, 14.20. $C_{17}H_{15}O_2N_3$ requires C, 69.62; H, 5.12; N, 14.33 per cent).

2-*Methyl*-3-(p-*aminophenyl*)-*quinazolone*-4.—2-Methyl-3-(*p*-acetylaminophenyl)-quinazolone-4(8 g.) was hydrolysed with 70% sulphuric acid (40 c.c.) in the same way as was done in the case of the corresponding analogue of the formyl series. The resulting base crystallised from 25% ethyl alcohol in shining plates, yield 6.0 g., m.p. 220°. (Found: N, 16.40. $C_{15}H_{13}ON_3$ requires N, 16.73 per cent).

2-*Methyl*-3-(p-*chloroacetylaminophenyl*)-*quinazolone*-4.—2-Methyl-3-(*p*-aminophenyl)-quinazolone-4 (1 g.) was chloroacetylated, using 1 c.c. of monochloroacetyl chloride, in the same manner as in the case of the corresponding analogue in the formyl series. The product crystallised from ethyl alcohol in glistening white plates, yield 0.8 g., m.p. 206° (decomp.). (Found: N, 12.60. $C_{17}H_{14}O_2N_3Cl$ requires N, 12.82 per cent).

2-*Methyl*-3-(p-*β-chloropropionylaminophenyl*)-*quinazolone*-4.—2-Methyl-3-(*p*-aminophenyl)-quinazolone-4 (1 g.) was chloropropionylated, using 1 c.c. of *β*-chloropropionyl chloride as the preceding compound in formyl series. Crystallisation from ethyl alcohol yielded shining white needles, yield 0.8 g., m.p. 222°. (Found: N, 12.10. $C_{18}H_{16}O_2N_3Cl$ requires N, 12.29 per cent.).

The above compound was then condensed with various amines like diethylamine, piperidine and diethanolamine. The diethylamine condensation products, however, could not be crystallised in any case as sticky products were obtained every time. Piperidine condensation product was obtained in well defined crystals. Diethanolamine condensation was successful in two cases but it failed in other cases. The condensation of 3-(*p*-chloroacetylaminophenyl)-quinazolone-4 with various amines could not be carried out due to the non-availability of raw materials. Results on these will, however, be reported in due course.

All the quinazolones listed in Table I have been prepared by the same method using 1 g. of the relevant chloro compound (VIII) and 2.5 moles of the amines. The mixture was heated in each case on a water-bath for 3 hours. The resulting product was

diluted with water, made alkaline with sodium carbonate, if not already alkaline, filtered, washed and dried. The condensation products were crystallised from solvents indicated in Table I.

TABLE I

Q stands for quinazolone-4.

No.	Name.	Crystallised from.	M.p.	Yield.	Formula.	Found.	Calc.
1.	3-(*p*-*β*-Piperidino-propionyl-aminophenyl)-Q.	EtOH	202°	1.1 g.	$C_{22}H_{24}O_2N_4$	C, 69.95 H, 6.33 N, 14.75	70.21 6.38 14.89
2.	3-(*p*-*β*-Diethanolaminopropionyl-aminophenyl)-Q	Do	120°	1.0	$C_{21}H_{24}O_4N_4$	C, 63.53 H, 6.14 N, 13.94	63.63 6.06 14.14
3.	2-Methyl-3-(*p*-*β*-piperidino-propionyl-aminophenyl)-Q	Do	200°	1.2	$C_{23}H_{26}O_2N_4$	N, 14.20	14.36
4.	2-Methyl-3-(*p*-piperidino-acetylaminophenyl)-Q	50% EtOH	140°	1.0	$C_{22}H_{24}O_2N_4$	C, 69.78 H, 6.18 N, 14.66	70.21 6.38 14.89
5.	2-Methyl-3-(*p*-diethanol-amino-acetylaminophenyl)-Q	EtOH	220°	1.0	$C_{21}H_{24}O_4N_4$	C, 63.47 H, 5.96 N, 14.29	63.63 6.06 14.14

The authors wish to express their thanks to Dr. S. M. Mukherji for kind interest in the work.

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PLANT ALKALOIDS. PART V. *BERBERIS LAMBERTII*, PARKER

By R. Chatterjee and A. Banerjee

Berberis lambertii, Parker has yielded oxyacanthine, berbamine, berberine, palmatine, jatrorrhizine and columbamine, and two bases, which appear to be hitherto unknown; they have been provisionally called lambertine ($C_{20}H_{19}O_4N$, m.p. 163°) and berlambine ($C_{20}H_{17}O_5N$, m.p. 199-200°).

Berberis lambertii is a shrub, one to two feet high, with yellow coloured shiny angled stems. It grows in Kumaon, at an altitude of 8000-9000 ft. from where the root of the plant was obtained for chemical examination and was identified by Dr S. K. Mukerjee, Curator of the Herbarium, Indian Botanic Garden, Calcutta. The root has furnished the usual *bis*benzyltetrahydro*iso*quinoline alkaloids, oxyacanthine and berbamine, the ammonium bases, berberine and palmatine and the phenolic bases, jatrorrhizine and columbamine. The root has further yielded two more bases, which appear to be hitherto unknown in Indian species of *Berberis*, and have been provisionally called lambertine, $C_{20}H_{19}O_4N$ and berlambine, $C_{20}H_{17}O_5N$.

Experimental

Well powdered air-dried roots (1 kg.) of *B. lambertii* were extracted with ethanol. The solvent was removed in *vacuo* and the sticky brown extract (100 g.) was treated with dilute acetic acid (50%, 60 c.c.) when most of it dissolved. The solution was filtered from sticky matter and was treated with ammonia and then extracted with ether (1000 c.c.).

Treatment of the Ether Extract.—The bulk of the ether solution was reduced to about 75 c.c. and shaken with concentrated hydrochloric acid. The acid solution was kept in the refrigerator when it deposited a yellow precipitate of hydrochloride of Base (A) (0.2 g.) which was filtered.

The residue of the hydrochloride of Base (A), which has been provisionally called lambertine, was crystallised from ethanol as shining needles which decomposed indefinitely. It contained three molecules of water of crystallisation. (Found: Cl, 8.4; H_2O, 12.65. $C_{20}H_{19}O_4N$, HCl, $3H_2O$ requires Cl, 8.29; H_2O, 12.63 per cent). [Found (in a sample dried *in vacuo*): C, 64.26; H, 5.11; N, 3.9; Cl, 9.1. $C_{20}H_{19}O_4N$, HCl requires C, 64.25; H, 5.09; N, 3.75; Cl, 9.49 per cent].

The yellow crystalline free base, lambertine, obtained in the usual manner from the hydrochloride, melted at 163°. [Found (a vacuum dried sample): C, 71.17; H, 5.6; N, 4.21. $C_{20}H_{19}O_4N$ requires C, 71.22; H, 5.64; N, 4.16 per cent].

The filtrate, obtained after the separation of lambertine hydrochloride, was treated carefully with potassium bromide when a sparingly soluble hydrobromide of a mixture of bases was precipitated, which was filtered. The free bases were liberated by treatment with ammonia and then treated with a well cooled saturated solution of sodium

sulphate in dilute sulphuric acid (30%); the precipitated sulphate of Base (B) was filtered and the filtrate was saturated with sodium nitrate to precipitate the nitrate of Base (C).

The free Base (B) was generated by treating the well cooled aqueous solution of the sulphate with ammonium hydroxide and was collected by extracting the free base with ether. On removal of the solvent ether, a few colorless crystals embedded in a thick syrup were obtained, which were kept in a refrigerator for two days, when the syrupy portion solidified as crystals; total yield, 0.01 g. The crude product was crystallised from methanol as colorless needles, m.p. 216° *in vacuo*. (Found: C, 73.1; H, 6.9; N, 4.6. Calc. for $C_{37}H_{40}O_6N_2$: C, 72.99; H, 6.6; N, 4.6 per cent). The needles did not depress the m.p. of oxyacanthine, m.p. 216° *in vacuo*, and gave all the colour reactions for oxyacanthine as described in the previous communication (this *Journal*, 1952, **29**, 921).

The free Base (C) was likewise generated by basifying its nitrate solution with ammonium hydroxide and extracting the free base with ether. The crude colorless crystals (0.01 g.) were purified by repeated crystallisations from methanol, m.p. 156° (decomp.). (Found: C, 72.9; H, 6.9; N, 4.5. Calc. for $C_{37}H_{40}O_6N_2$: C, 72.99; H, 6.6; N, 4.6 per cent). The m.p. and colour reactions of the Base (C) indicated it to be berbamine, which was confirmed by mixing the base with an authentic sample of berbamine and determining the m.p. 156° (decomp.).

The ether solution, now free from bases (A, B and C), yielded on evaporation a yellow coloured residue, Base (D) (0.1 g.) which crystallised as golden yellow needles from acetone, m.p. 199°-200°. This base had been provisionally called berlambine. Its crystals are sparingly soluble in ethanol and benzene, almost insoluble in petroleum ether (b. p. 60°-80°) and water, soluble in hot acetic acid from which berlambine could be crystallised. (Found: C, 68.48; H, 5.04; N, 3.95. $C_{20}H_{17}O_5N$ requires C, 68.37; H, 4.84; N, 3.99 per cent). Berlambine is readily soluble in an ethanolic solution of dry hydrogen chloride. The unstable hydrochloride was obtained as a pale yellow residue on evaporation of ethanol.

Treatment of the Aqueous Layer.—The aqueous ammoniacal mother-liquor (300 c.c.), left after ether extraction, was treated with charcoal and filtered; the clear brown coloured filtrate was acidified with hydrochloric acid to give an 1% solution and allowed to stand overnight in an ice box when yellow coloured crystals (0.2 g.) were obtained. These were filtered and purified by repeated crystallisations from ethanol and then a portion was made alkaline with sodium hydroxide solution (10%) and mixed with acetone, warmed to 50° and allowed to stand to obtain lemon-yellow crystals, m.p. 168-69° (decomp.) which did not depress the m. p. of berberine acetone, 168° (decomp.).

The other portion was dissolved in water and treated with chloroplatinic acid, the insoluble berberine chloroplatinate was purified by repeated washing with water till free from hydrochloric acid. [Found: Pt, 18.0. Calc. for $(C_{20}H_{17}O_4N)_2$, H_2PtCl_6: Pt, 18.02 per cent].

The brown coloured filtrate (300 c.c.) was warmed with charcoal and filtered from it and then treated with concentrated hydrochloric acid (20 c.c.) and glacial acetic acid (30 c.c.) and zinc powder in small instalments, till the brown colour of the solution

became pale yellow. The solution was freed from unchanged zinc, cooled and treated with excess of ammonia to redissolve the precipitated zinc hydroxide, and then the ammoniacal solution was extracted carefully with ether (1000 c.c.). The ether solution was then treated with sodium hydroxide solution (5%, 40 c.c.) when a dark brown alkaline layer separated; it contained phenolic bases.

The residue (0.04 g.) obtained on removal of ether was crystallised from methanol as colorless needles, m.p. 144°, no depression in m.p. when mixed with tetrahydropalmatine, m.p. 144°. (Found: C, 70.7; H, 7.1; N, 3.8. Calc. for $C_{21}H_{25}O_4N$: C, 70.98; H, 7.04; N, 3.94 per cent).

The dark coloured alkaline solution was ice cooled, acidified and then made ammoniacal and the mixture of crude phenolic bases was dissolved in methanol and oxidised with iodine; fractional crystallisation separated crystals of m.p. 210-12°, which did not depress the m.p. of jatrorrhizine iodide, m.p. 210-12°, and of m.p. 223-24° which did not depress the m.p. of columbamine iodide, m.p. 223-24°.

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ON THE APPLICATION OF ANDRADE'S VISCOSITY EQUATION TO SUPERSATURATED AQUEOUS SOLUTIONS

By Ram Gopal

The equation of Andrade, viz., $\log \eta = A + B/T$, has been found to be applicable to supersaturated aqueous solutions of electrolytes, e.g. KCl, KBr, KI, KNO_3, etc., which dissolve in water to give only slightly viscous solutions. It does not apply in solutions of electrolytes of the type $MgSO_4$, K-acetate, Na-acetate, etc., which yield viscous solutions on dissolution in water.

Several empirical, semi-empirical and theoretically derived relationships connecting viscosity and temperature have been proposed from time to time (cf. Srinivasan and Prasad, *Phil. Mag.*, 1942, *vii*, **33**, 258). Out of these the equation of Andrade,

$$\eta = A' e^{B'/RT} \quad \text{or} \quad \log \eta = A + B/T$$

has been found to be most theoretically sound and simple to handle (cf. Srinivasan and Prasad, *loc. cit.* Reports of Progress in Physics, 1935, ii, 16; *Ann. Chem Rep.*, 1937, p. 81). This equation, although meant for pure non-associated liquids, has been found to hold good in a number of aqueous solutions by Berl, Umstätter and Karrer (*Z. physikal. Chem.*, 1931, **150**, 284) and by Joshi and Solanki (this *Journal*, 1940, **17**, 630). With this successful application of Andrade's equation to unsaturated aqueous solutions, it was considered desirable to find out how far this equation would hold good in supersaturated aqueous solutions.

Experimental

The viscosity of supersaturated solutions was determined by the method of Scarpa (*Gazzetta*, 1910, **40**, 271) as modified by Farrow (*J. Chem. Soc.*, 1912, **101**, 347) and Taimini (*J. Phys. Chem.*, 1928, **32**, 604). Data obtained have been omitted here for the sake of brevity. From the data (this *Journal*, 1947, **24**, 455) viscosity-temperature and log viscosity-$1/T$ curves were drawn. These curves lead to the following general conclusions:

(*i*) Viscosity temperature ($\eta - t$) curves have a marked positive curvature without exception (Fig. 1) but show no abrupt change in viscosity at the saturation temperature. Thus, the results obtained here lend support to the views of Nichol (*J. Chem. Soc.*, 1879, **6**, 28) and Taimini (*loc. cit.*) *i.e.*, there is no sudden change in the viscosity of a solution when it passes from the unsaturated into the supersaturated condition.

(*ii*) The plot of log η against $1/T$ gives a very close approach to linearity in many cases, e.g. in solutions of KI, KBr, KCl, KNO_3, $BaCl_2$, $Ba(NO_3)_2$, etc. (Fig. 2). Devia-

tions from linearity are very much marked in solutions of $MgSO_4$, Na-acetate, K-acetate, tartaric acid, citric acid, etc. (Fig. 3). The former solutions have a comparatively low viscosity, while the latter are highly viscous. In some cases, e.g. NH_4NO_3, the plot appears to be straight line at lower concentrations, but at higher concentrations the curves have a slight positive curvature.

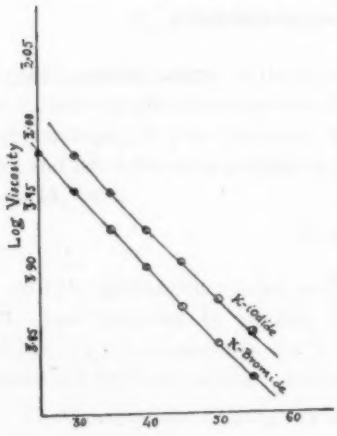
Discussion

From the above description it appears that the equation of Andrade,

$$\log \eta = A + B/T$$

holds in cases of solutions of electrolytes which dissolve in water to give solutions of comparatively low viscosity, whereas it fails completely in viscous solutions. It is a well known fact that, in general, the solutions of high viscosity are those in which the solute has a great affinity for the solvent molecules, and as a result, the solvent molecules associate themselves with the ions and molecules of the solute forming solvates. These solvates break up gradually as the temperature is raised. This consequently invalidates the equation of Andrade for such solutions. But in cases where the equation holds, the the solutes have, in general, little affinity for water molecules, and hence, no appreciable solvation occurs. Obviously, no significant structural changes would occur when the temperature is varied in such cases, at least within the limited range of temperatures studied here.

Fig. 1



Some interesting results are brought to light when one plots log η against $1/T$ for water itself (one can use the data of Hosking, *Phil. Mag.*, 1909, **1**, 50; **2**, 260). The curve is clearly found to have a slight but definite positive curvature (Fig. 2), whereas aqueous solutions of strong electrolytes, of the first type mentioned above, give almost a straight line for log $\eta - 1/T$. It appears at first a very disconcerting anomaly. Water ordinarily consists of complex molecules, the complexity becoming lesser at higher temperatures (cf. *J. Chem. Phys.*, 1939, **7**, 869; *Trans Faraday Soc.*, 1944, **40**, 184; Kortüm-Bockris, "Electrochemistry", 1951, p. 183) and *vice versa*. Consequently, the equation of Andrade does not hold good as in associated liquids, and log $\eta - 1/T$ plot has a positive curvature. When an electrolyte is dissolved, depolymerisation of water molecular complexes * occurs (*J. Chem. Soc.*, 1910, **97**, 2000), and now the simpler molecules are present instead of complex ones. If the electrolyte added has not appreciable affinity for water molecules, the equation of Andrade should hold as no complexes are present in the system which could be broken up by the rise in temperature. This is actually found to be the case and the equation holds in electrolytic solutions of

* See foot note, p. 710.

lower viscosity. Thus, these observations lend support to the depolymerisation hypothesis of water molecular aggregates* in presence of changed particles.

FIG. 2

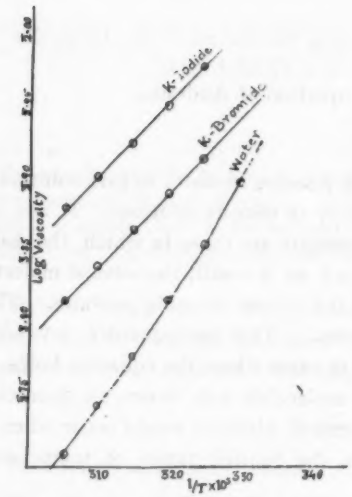
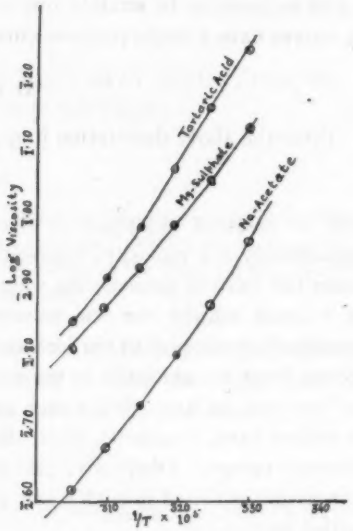


FIG. 3



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** There is overwhelming evidence in support of this hypothesis in the literature (see Kortüm-Bockris, *loc. cit.*).

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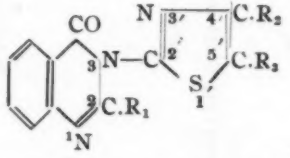
STUDIES IN THERAPEUTICS. PART I

By Megh Kumar Jain and K. S. Narang

Some 3-thiazolyl-4-quinazolones have been prepared with a view to testing their physiological properties.

The thiazole ring system has, of late, assumed considerable importance by virtue of its presence in a good many physiologically important compounds, namely, Thiamin, Pencillin, etc. The quinazolone ring system is also equally, if not more, important as it is present in alkaloids like vasicine, and antimalarials like febrifugine and arborine. It was therefore considered of interest to synthesise a few 3-thiazolyl-4-quinazolones containing suitable biologically important functional groupings in suitable positions.

The present communication records the synthesis of the compounds of type (I).



(I, where R_1=H or Me; R_2 and R_3 are different substituents).

The general scheme of the synthesis in the present series consists in heating together the various 2-aminothiazoles with the suitable 3:1:4-benzoxazones. The formation of the 4-quinazolone, it may be noted, is an one step-process starting from the 3:1:4-benzoxazone and not a two-step process as found by Zentmeyer and Wagner (*J. Org. Chem.*, 1949, **14**, 967).

Experimental

All the quinazolones listed in Table I, except as stated otherwise in the experimental part, were prepared by heating together equivalent amounts of the 2-aminothiazole and the 3:1:4-benzoxazones for 4 hours on a water-bath. The resulting products were crystallised from the solvents, indicated in Table I.

The compounds bearing an asterisk mark in Table I were prepared with a slight modification in the general method given above. Equivalent amounts of the 3:1:4-benzoxazone and the 2-aminothiazole were heated at 130°-140° for 3 hours and then worked up as before.

The compound having No. 5 in Table I was prepared by introducing still another modification. Here equivalent amounts of the reactants were taken in a small amount of dry benzene and then heated at 130°-150° for 3 hours. This ensured a more uniform mixing of the reactants.

TABLE I

Compounds of type (I).

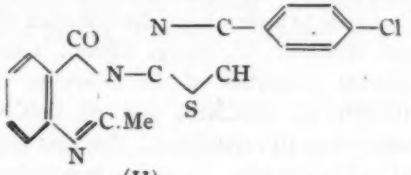
No.	Substituents. R_1.	R_2.	R_3.	** Name.	Crystallised. from	M. p.	Yield.	Formula.	Found.	Calc.
1.	$-CH_3$	$-CH_3$	$-H$	2-Methyl-3-(4′-methyl-T)-Q	Benzene	148°	78.1%	$C_{13}H_{11}ON_3S$	N, 16.10%	16.34%
2.	$-CH_3$	$-CH_3$	$-CH_3$	2-Methyl-3-(4′:5′-dimethyl-T)-Q	,,	200°	71.4	$C_{14}H_{13}ON_3S$	N, 15.20	15.49
* 3.	$-CH_3$	$-C_2H_5$	$-H$	2-Methyl-3-(4′-ethyl-T)-Q	,,	201°	71.4	$C_{14}H_{13}ON_3S$	N, 15.10	15.49
* 4.	$-CH_3$	$-C_6H_5$	$-H$	2-Methyl-3-(4′-phenyl-T)-Q	,,	144°	69.4	$C_{18}H_{13}ON_3S$	N, 12.90	13.16
5.	$-CH_3$	$-C_6H_4Cl$ (*p*)	$-H$	2-Methyl-3-(4′-*p*-chlorophenyl-T)-Q	Ethyl acetate	204°	70.0	$C_{18}H_{12}ON_3SCl$	N, 11.70	11.8
* 6	$-CH_3$	$-C_6H_4OCH_3$ (*p*)	$-H$	2-Methyl-3-(4′-*p*-methoxyphenyl-T)-Q	EtOH	160°	68.1	$C_{19}H_{15}O_2N_3S$	C, 65.27 H, 4.60 N, 12.20	65.32 4.29 12.03
7.	$-H$	$-CH_3$	$-H$	3-(4′-Methyl-T)-Q	,,	184°	76.4	$C_{13}H_9ON_3S$	N, 17.10	17.28
8.	$-H$	$-CH_3$	$-CH_3$	3-(4′:5-Dimethyl-T)-Q	,,	202°	77 7	$C_{13}H_{11}ON_3S$	N, 16.29	16.34
* 9.	$-H$	$-C_6H_5$	$-H$	3-(4′-Phenyl-T)-Q	Benzene	162°	68.2	$C_{17}H_{11}ON_4S$	N, 13.48	13.77
10.	$-H$	$-C_6H_4Cl$ (*p*)	$-H$	3-(4′-*p*-Chlorophenyl-T)-Q	C_6H_6-Pet. ether	172°	62 5	$C_{17}H_{10}NN_3SCl$	N, 12.00	12.04
11.	$-H$	$-C_6H_4(O(p)CH_3)$	$-H$	3-(4′-*p*-Methoxyphenyl-T)-Q	,,	182°	62.5	$C_{18}H_{12}O_2N_3S$	N, 12.64	12.54
12.	$-CH_3$	$-CH_3$	$-CO_2Et$	2-Methyl-3-(4′-methyl-5′-carbethoxy-T)-Q	EtOH	235°	60.0	$C_{16}H_{15}O_3N_3S$	C, 58.10 H, 4.76 N, 12.48	58 35 4.56 12.76

** Q stands for quinozolone-4 and and T for thiazolyl.

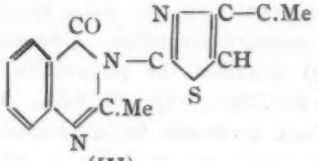
In the synthesis of the compound No. 12, equivalent amounts of the reactants were first of all gradually raised to a temperature of 170° when the whole mass fused. The temperature was then lowered to 130°-140° and maintained there for 1½ hours. The end of the reaction was indicated by complete solidification of the reaction mixture.

Biological Activity Results

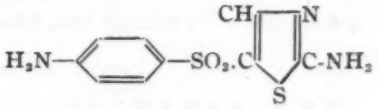
Compounds (II) and (III), when tested against *Mycobacterium tuberculosis in vitro*, were found active up to 1 in 1000. It may be noted, however, that it is not necessary that a compound which is relatively less active *in vitro* must necessarily be so *in vitro* too. In fact, literature records a number of instances of the compounds which are very active *in vitro* but relatively less active *in vitro* (Hoggarth, *Brit. J. Pharmacol. Chemotherap.*, 1948, **3**, 146). Promizole (IV) is one such instance which shows activity *in vitro* only up to 1 in 1000 but is very active *in vivo*.



(II)



(III)



(IV)

Reports on the activity of some of the compounds in other fields are expected shortly and the results will be communicated later.

The authors wish to express their thanks to Dr. S. M. Mukherji for his kind interest in the work, and also to Dr. B. Mukerji, Director, Central Drug Research Institute, Lucknow, for his kind permission to get the compounds tested against *Mycobacterium tuberculosis in vitro*.

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QUINOLINE COMPLEXES OF THIOCYANATES OF ZINC, CADMIUM, NICKEL AND COBALT

By G. C. Bhattacharya and P. C. Sinha

Preparation and properties of the quinoline complexes of the thiocyanates of the bivalent metals, zinc, cadmium, nickel and cobalt have been described. Heats of formation of these complexes have been determined by thermochemical measurements and their stability has been discussed.

The preparation, properties and a study of stability of the complexes formed by quinoline with the sulphates of zinc, cadmium, nickel and cobalt have been described in two previous papers (this *Journal*, 1950, **27**, 21 ; 1953, **30**, 485). The present paper deals with preparation, properties and stability of the quinoline complexes of the thiocyanates of the same metals with a view to ascertaining the influence of the anion in complex formation. Grossmann and Hünseler (*Z. anorg. Chem.*, 1905, **46**, 375, 385) described the preparation and general properties of the following complexes : $2Q.Zn(CNS)_2$, $3Q.Cd(CNS)_2$, $2Q.Cd(CNS)_2$, $4Q.Ni(CNS)_2$ and $2Q.Co(CNS)_2.2H_2O$ (where Q stands for quinoline). Those were all crystalline. The zinc and cadmium compounds are insoluble in ether and while the zinc compound is soluble in alcohol, the cadmium complexes are insoluble in it. Both the nickel and cobalt complexes were found to be soluble in water and alcohol. No attempt was, however, made to determine the stability of these complexes.

Experimental

As the thiocyanates of the metals were readily soluble in hot quinoline, the preparation of the complexes offered no difficulty. The thiocyanate (2 to 4 g.) was dissolved in 20 to 30 g. of quinoline by gentle heating. On cooling, well defined crystals separated in each case. These were collected in a Buchner funnel, washed thoroughly with ether and dried between folds of filter paper. The methods of estimation of quinoline and the metals have been described in the previous papers (*loc. cit.*). The thiocyanate was estimated gravimetrically as silver thiocyanate. The results of analyses are recorded in Table I.

Table I

	$2Q.Zn(CNS)_2$.		$3Q.Cd(CNS)_2$.		$3Q.Co(CNS)_2$.		$4Q.Ni(CNS)_2$.	
	Found. (mean of 3).	Calc.	Found. (mean of 3).	Calc.	Found. (mean of 3).	Calc.	Found. (mean of 3).	Calc.
M	14.6%	14.0%	17.9%	18.3%	11.2%	10.5%	8.4%	8.5%
Q	56.3	58.7	60.4	62.9	67.0	68.9	73.2	74.7
CNS	25.1	26.4	18.8	18.8	21.1	20.7	17.1	16.8

[Q = quinoline and M = Zn or Cd or Co or Ni]

The complexes obtained appear to argee generally in composition with those obtained by previous workers except that only one complex is obtained with cadmium

thiocyanate and that the cobalt complex obtained in the present work do not contain any water and the formula is entirely different.

Among the various physical methods employed for obtaining a measure of the stability of complex compounds, determinations of dissociation pressures at various temperatures as well as measurements of heat of formation by thermo-chemical methods have been used extensively. The first method was found to be inapplicable in the case of the thiocyanate complexes since the dissocation presures up to 120° was too low to be measured with any degree of accuracy. The heats of formation of the complexes were therefore determined calorimetrically. The calorimeter used and the method employed were the same as described in a previous paper (*loc. cit.*). The heat capacity of the system was determined with 150 c.c. of 6*N* sulphuric acid in the calorimeter using a measured input of heat by means of nichrome coil and was verified by neutralisation experiments. Heats of reaction of an accurately weighed quantity of the complex compounds and of the thiocyanates of the metals were determined using the same volume of 6*N* sulphuric acid after making the usual corrections for the heating effect of stirring and for loss of heat by radiation. The results obtained are shown in Table II.

TABLE II

Average value of thermal capacity of the system = 158.2 cal./degree.

Substance.	Wt. of substance.	Temp. change (corr.).	Heat of reaction (G. F. W.). (cals.).	Mean heat of formation (G. F. W.).
$Zn(CNS)_2$	2.2266 g	−0.082°	−1,057	−1,024 cals.
	2.1642	−0.075	− 994	
	2.0572	−0.074	−1,023	
$Cd(CNS)_2$	0.7665	−0.128	−6,036	−6,070
	0.7861	−0.133	−6,205	
	0.9200	−0.152	−5,970	
$Ni(CNS)_2$	1.5110	−0.055	−1,006	−1,019
	1.9400	−c.072	−1,026	
	1.9411	−0.072	−1,025	
$Co(CNS)_2.4H_2O$	1.0605	Negligible	Negligible	0
	1 5899	,,	,,	
	2.2149	,,	,,	
$Zn(CNS)_2.2Q$	1.1260	−0.088	−5,433	−5,442+16,978
	1.5621	−0.121	−5,384	
	1.1450	−0.c98	−5,511	
$Cd(CNS)_2.3Q$	1.3760	−0.059	−4,177	−4,090+16,860
	1.3759	−0.059	−4,180	
	1.1264	−0.052	−3,914	
$Ni(CNS)_2.4Q$	1.5866	−0.030	−2,060	−2,025+26,126
	2.0720	−0.038	−2,004	
	1.6295	−0.030	−2,007	
$Co(CNS)_2.3Q$	1.3490	+0.068	+4.499	+4,530+14,310
	1.4129	+0.072	+4,53I	
	1.4621	+0.075	+4,561	

By Hess's law the heat of formation of the complex is $Q_3 + nQ_2 - Q_1$, in which Q_1, Q_2 and Q_3 represent the heats of reaction of the complex, quinoline and the thiocyanates respectively with $6N$ sulphuric acid and n denotes the number of molecules of quinoline in the complex. When the heats of formation of the complexes are calculated from the data recorded in Table II and the heat of reaction of quinoline (Q_2) determined previously being 6,280 cal./G.F.W., the heats of formation of the complexes, $Zn(CNS)_2.2Q$, $Cd(CNS)_2.3Q$, $Ni(CNS)_2.4Q$ and $Co(CNS)_2.3Q$, work out as +16, 978, +16,860, +26,126 and +14,310 cal./G.F.W. respectively.

DISCUSSION

It will be seen that the stability the quinoline thiocyanate complexes is in the order: $Ni(CNS)_2.4Q$, $Zn(CNS)_2.2Q$, $Cd(CNS)_2.3Q$, $Co(CNS)_2.3Q$, while the stability of quinoline complexes of the sulphates of the corresponding metals follow the order: $NiSO_4.3Q.4H_2O$, $CdSO_4.2Q.6H_2O$, $CoSO_4.1Q.6H_2O$, $ZnSO_4.2Q.8H_2O$. Measurements of heats of formation show that quinoline complexes of the thiocyanates are more stable than the quinoline complexes of the sulphates of the corresponding metals, indicating that the bivalent sulphate anion exerts a retarding effect on the cation in forming complexes. It supports the view put forward by Chang and Yü (*Z. anorg. Chem.*, 1939, **243**, 14) that the presence of multivalent anion decreases the tendency of bivalent metals to form complexes.

The relative size of the cation and anion is an important factor which determines the stability of the complex. The difference in volume between the cations Zn^{2+} and Cd^{2+} and the sulphate anion SO_4^{2-} is greater than that between these cations and the thiocyanate anion. It is therefore expected that the cations would be able to take up a larger number of addenda and would be more stable in presence of the sulphate anion than when the thiocyanate anion is present. Experimental results, however, are contrary to this expectation. It seemes that the anomalous behaviour is due to the spatial arrangement of the atoms in the anions. While the sulphate ions possess a tetrahedral structure, the thiocyanates are linear. It appears that in the process of crystallisation the more compact tetrahedral sulphate ions occupy more of the available space round the metal atom, squeezing out the addenda molecules of quinoline than their corresponding thiocyanates.

It must be mentioned that the heat of formation of the cobalt complex could not be determined from its anhydrous salt as the data for the heat of reaction in dilute sulphuric acid or the heat of solution in water of the anhydrous $Co(CNS)_2$ are not known. A sample of anhydrous $Co(CNS)_2$ was prepared and attempts were made to determine its heat of reaction with $6N$ sulphuric acid but its rate of dissolution was found to be too slow to allow the measurement of thermal effect with any degree of precision.

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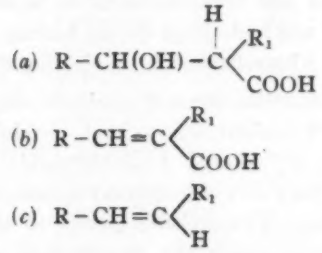
CONDENSATION OF AROMATIC ALDEHYDES WITH MALON-*o*-, *m*-, *p*-TOLUIDIC ACIDS. PART I. WITH BENZALDEHYDE, *o*-, *m*-, *p*-HYDROXY- AND -METHOXYBENZALDEHYDES

By P. I. Ittyerah and Kantilal C. Pandya

Malon-*o*-, *m*- and *p*-toluidic acids were condensed with benzaldehyde, the three monohydroxy- and the three monomethoxybenzaldehydes. A trace of either pyridine or piperidine was found to catalyse the reactions. Salicylaldehyde gave the corresponding coumarin-3-carboxytoluidides. The other aldehydes gave the corresponding hydroxy- and methoxy-benzylidenemalon-toluidic acids and the corresponding hydroxy- and methoxy-cannam-toluidides. The methoxybenzaldehydes showed far greater reactivity than the hydroxybenzaldehydes.

In two earlier papers Ittyerah and Pandya (*Proc. Ind. Acad. Sci.*, 1941, **13A**, 119, 461) had reported the condensation of malonanilic acid with *o*-, *m*- and *p*-hydroxy- and three monomethoxybenzaldehydes. Now these aldehydes have been condensed with malon-*o*-, *m*- and *p*-toluidic acids.

Malon-*o*-, *m*- and *p*-toluidic acids were prepared according to the method given by Chattaway and Olmsted (*J. Chem. Soc.*, 1910, **97**, 939). The condensation of these acids with aromatic aldehydes may yield the following products:



[where R = aryl radical, R_1 = -$CONHC_6H_4(CH_3)$; (CH_3) may be *o*, *m* or *p*].

The aldol (*a*) may be taken as the necessary intermediate as would be in keeping with the generally accepted views (*Ann. Reports, Chem. Soc.*, 1939, p. 210), though in these condensations it has never been separated. The products (*b*) and (*c*) are, however, stable and easily isolated. The yields of these two vary much according to the conditions under which the experiments are carried out as well as according to the nature of the aldehydes. Thus, when a trace of pyridine or piperidine is used as a condensing agent, decarboxylation is induced, and (*c*) is the main product. Higher temperatures also favour decarboxylation. On the other hand, when the condensation is carried out at 100° or at a lower temperature, or when condensing agents are absent or when glacial acetic acid is used as a condensing agent, (*b*) is the main product.

A trace of pyridine or piperidine acts as a catalytic agent. The maximum yields in all cases were obtained with pyridine or with piperidine; sometimes the yields were

theoretical. This is in agreement with earlier observations made in this laboratory in the condensation of malonic acid with aromatic aldehydes in the presence of pyridine (Pandya and co-workers, Parts III to XIII: *Proc. Ind. Acad. Sci.*, this *Journal*, and *J. Univ. Bombay*) and also in the condensation of malonanilic acid with aromatic aldehydes (Pandya and co-workers, Parts I to VII : *Proc. Ind. Acad. Sci.*, and *Proc. Nat. Acad. Sci., India*).

Attention has already been drawn to the retarding influence of the hydroxyl group, which, when present in the aldehyde molecule, lowers the yields of the corresponding cinnamic derivatives. It has also been observed that the yields become much better and in some cases, almost quantitative, when the hydroxyl group is replaced by a methoxyl group. In the present paper similar observations have been made in the condensation of the three monohydroxy- and the three monomethoxy-benzaldehydes with malon-*o*-, *m*- and *p*-toluidic acids.

Unlike other aldehydes, salicylaldehyde gave the corresponding coumarin-3-carboxytoluidides. They are all yellow crystalline substances. No products of the type (*b*) or (*c*) could be isolated. Salicylaldehyde has already been condensed with malon-*o*- and *m*-toluidic acids by Ahluwalia, Haq and Ray (*J. Chem. Soc.*, 1931, 2059). They took a pyridine mixture (3 mols. and a trace respectively) and did not anywhere mention the yield. In the condensation of malon-*p*-toluidic acid with salicylaldehyde in the presence of a trace of piperidine, in addition to the expected coumarin-3-carboxy-*p*-toluidide, a deep orange coloured substance melting at 96° was also isolated. This gave a deep violet coloration with ferric chloride and was identified to be *o*-hydroxybenzal-*p*-toluidine. Probably malon-*p*-toluidic acid was hydrolysed during heating and the *p*-toluidine, then formed, might have condensed with salicylaldehyde yielding the above product.

Another point noted was regarding the acid products obtained in the condensation of *p*-hydroxybenzaldehyde with malon- *o*-, *m*- and *p*-toluidic acids. The yields of *p*-hydroxybenzylidene-malon- *o*-, *m*- and *p*-toluidic acids were only 20%, 13.5% and 27% respectively. But the yields of *p*-hydroxycinnam-*o*-, *m*- and *p*-toluidides were 86%, 79% and 94% respectively. This probably points to the unstable nature of the acid products referred to above, under the experimental conditions observed in these condensations.

Best yields obtained, when salicylaldehyde was condensed with malon-*o*-, *m*- and *p*-toluidic acids, were 43.1% coumarin-3-carboxy-*o*-toluidide, 32.3% coumarin-3-carboxy-*m*-toluidide and 28.7% coumarin-3 carboxy-*p*-toluidide (Table I). On the other hand, *o*-methoxybenzaldehyde has yielded 97.4% *o*-methoxycinnam-*o*-, *m*- and *p*-toluidides. Similarly *p*-methoxybenzaldehyde has shown a greater reactivity than *p*-hydroxybenzaldehyde (Table I). *m*-Methoxybenzaldehyde behaved in a slightly different manner. It showed a greater reactivity than *m*-hydroxybenzaldehyde when it condensed with malon-*o*- and *m*-toluidic acids. With malon-*p*-toluidic acid, it has given lower yields.

Experimental

The general pocedure had been to mix equimolecular quantities of the acid and the aldehyde in a small r. b. flask and then heat it on a water-bath. When either a trace of

pyridine or piperidine was used as a condensing agent, the base was added in 0.15 molar proportion. After heating for the required length of time (generally 4 hours but in some cases only 1 hour), the contents of the flask were extracted with a strong solution of sodium bicarbonate. The acid products were dissolved by the alkali. The non-acid residue left was filtered and purified by recrystallisation from suitable organic solvents like alcohol, acetone and benzene. The alkali extract on acidifying with strong hydrochloric acid yielded the acid products which were further purified by recrystallisation from alcohol or acetone. All the products except those obtained from salicylaldehyde were white crystalline compounds. Salicylaldehyde products were yellow in colour.

All the products were analysed and identified. The results are shown in Table 1.

TABLE I

No.	*Product.	Formula.	M. p.	Yield.	% Nitrogen. Found.	% Nitrogen. Calc.	Silver salt (Ag %). Found.	Silver salt (Ag %). Calc.
1.	Benzylidene-malon-*o*-T	$C_{17}H_{15}O_3N$	201°	92.8 %	5.25	4 98	27.50	27.83
2.	Cinnam-*o*-toluidide	$C_{16}H_{15}ON$	170°	100.0	6.1	5.90		
3.	Benzylidene-malon-*m*-T	$C_{17}H_{15}O_3N$	196°	74.7	5.03	4.93	27.94	27.83
4.	Cinnam-*m*-toluidide	$C_{16}H_{15}ON$	114°	92.8	6.1	5.90		
5.	Benzylidene-malon-*p*-T	$C_{17}H_{15}O_3N$	228°	78.3	5.1	4.98	27.60	27.83
6.	Cinnam-*p*-toluidide	$C_{16}H_{15}ON$	162°	92.8	6.03	5.90		
7.	Coumarin-3-carboxy-*o*-Toluidide	$C_{17}H_{13}O_3N$	226°	43.1	5 01	5.02		
8.	Coumarin-3-carboxy-*m*- ,,	$C_{17}H_{13}O_3N$	202°	32.3	5.13	5.02		
9.	Coumarin-3-carboxy-*p*- ,,	$C_{17}H_{13}O_3N$	230°	28.7	5 12	5.02		
10.	*m*-OH-benzylidene-malon-*o*-T	$C_{17}H_{15}O_4N$	210°	50.5	4 88	4.71	26.50	26.72
11.	*m*-OH-cinnam-*o*-toluidide	$C_{16}H_{15}O_2N$	210°	79 5	5 63	5.53		
12.	*m*-OH-benzylidene-ma'on-*m*-T	$C_{17}H_{15}O_4N$	181°	53.8	4.82	4.71		
13.	*m*-OH-cinnam-*m*-toluidide	$C_{16}H_{15}O_2N$	180°	94.8	5.71	5.53		
14	*m*-OH-benzylidene-malon-*p*-T	$C_{17}H_{15}O_4N$	216°	64 0	5.09	4.71	26.50	26.72
15.	*m*-OH-cinnam-*p*-toluidide	$C_{16}H_{15}O_2N$	209°	94.8	5.69	5.53		
16.	*p*-OH-benzylidene-malon-*o*-T	$C_{17}H_{15}O_4N$	227°	20.2	4.89	4.71		
17.	*p*-OH-cinnam-*o*-toluidide	$C_{16}H_{15}O_2N$	220°	86.6	5.73	5.53		
18.	*p*-OH-benzylidene-malon-*m*-T	$C_{17}H_{15}O_4N$	213°	13.5	4.90	4.72		
19.	*p*-OH-cinnam-*m*-toluidide	$C_{16}H_{15}O_2N$	205°	79.0	5.56	5.53		
20.	*p*-OH-benzylidene-malon-*p*-T	$C_{17}H_{15}O_4N$	160°	27.0	4.98	4.71	26.46	26.72
21.	*p*-OH-cinnam-*p*-toluidide	$C_{16}H_{15}O_2N$	210°	94.8	5.60	5.53		
22.	*o*-MeO-benzylidene-malon-*o*-T	$C_{18}H_{17}O_4N$	212°	41.8	4.73	4.53	25.89	25.83
23.	*o*-MeO-cinnam-*o*-toluidide	$C_{17}H_{17}O_2N$	164°	97.4	5.36	5.20		
24.	*o*-MeO-benzylidene-malon-*m*-T	$C_{18}H_{17}O_4N$	231°	70.7	4.80	4.53	25.84	25.83
25.	*o*-MeO-cinnam-*m*-toluidide	$C_{17}H_{17}O_2N$	141°	97.4	5.41	5.20		
26.	*o*-MeO-benzylidene-malon-*p*-T	$C_{18}H_{17}O_4N$	223°	57.9	4.61	4.53	26.36	25 83
27.	*o*-MeO-cinnam-*p*-toluidide	$C_{17}H_{17}O_2N$	177°	97.4	5.28	5.20	26 36	25.83
28.	*m*-MeO-benzylidene-malon-*o*-T	$C_{18}H_{17}O_4N$	185°	57.9	4 79	4.53		
29.	*m*-MeO-cinnam-*o*-toluidide	$C_{17}H_{17}O_2N$	117°	89.8	5.47	5 20		
30.	*m*-MeO-benzylidene-malon-*m*-T	$C_{18}H_{17}O_4N$	172°	64.3	4 58	4.53	25.70	25.83
31.	*m*-MeO-cinnam-*m*-toluidide	$C_{17}H_{17}O_2N$	108°	97.4	5 36	5.20		
32.	*m*-MeO-benzylidene-malon-*p*-T	$C_{18}H_{17}O_4N$	171°	64.3	4.60	4.53	25.65	25.83
33.	*m*-MeO-cinnam-*p*-toluidide	$C_{17}H_{17}O_2N$	107°	74.9	5.53	5.20		
34.	*p*-MeO-benzylidene-malon-*o*-T	$C_{18}H_{17}O_4N$	217°	96.5	4 50	4.53		
35.	*p*-MeO-cinnam-*o*-toluidide	$C_{17}H_{17}O_2N$	177°	97.4	5.30	5.20		
36.	*p*-MeO-benzylidene-malon-*m*-T	$C_{18}H_{17}O_4N$	203°	57.9	4.76	4.53	25.69	25.83
37.	*p*-MeO-cinnam-*m*-toluidide	$C_{17}H_{17}O_2N$	108°	97.4	5.23	5.20		
38.	*p*-MeO-benzylidene-malon-*p*-T	$C_{18}H_{17}O_4N$	205°	45.0	4.61	4.53	25.46	25.83
39.	*p*-MeO-cinnam-*p*-toluidide	$C_{17}H_{17}O_2N$	158°	97.4	5.31	5.20		

* T stands for toluidic acid.

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STUDIES ON THE FRIES REARRANGEMENT. PART X

By A. B. Sen and S. S. Parmar

Fries rearrangement of four esters of crotonic acid and the effect of temperature and solvent on the course of the Fries rearrangement have been studied.

In continuation of our work on Fries rearrangement (Sen and Misra, this *Journal*, 1949, **26**, 339; Sen and Parmar, *ibid.*, 1951, **28**, 661) we have now extended the work to four more esters of crotonic acid. The rearrangement was carried out at 120° (without solvent) using 1.3 to 1.5 moles of anhydrous aluminium chloride, when only *o*-hydroxyketones were obtained. The mother-liquor after removal of the *o*-hydroxyketone in two cases was worked up for the *para* isomer, which was found absent. The hydroxyketones obtained conformed to Pyman's test (*J. Chem. Soc.*, 1930, 280) for *o*-hydroxyketones and were characterised through their 2:4-dinitrophenylhydrazones. The temperature effect has been studied with the acetates of thymol, carvacrol, *m*-ethylphenol and 3:5-dimethylphenol and crotonates of thymol and carvacrol at 100°, 120°, 140° and 160°, using 1.3 to 1.5 moles of anhydrous aluminium chloride in the absence of any solvent. The optimum temperature arrived at in all the six cases was 120°, when the yield of the *o*-hydroxyketones was maximum. The higher temperature resulted in charring and a considerable reduction in the yields. The effect of solvent using CS_2, nitrobenzene, toluene and xylene has been studied with the acetates of thymol, carvacrol, *m*-ethylphenol and 3:5-dimethylphenol and crotonates of *p-tert.* butylphenol and resorcinol monomethyl ether (Sen and Parmar, *loc. cit.*). It has been observed that the presence of solvent offers no advantage except that nitrobenzene lowers the temperature of the reaction (Sen and Misra, *loc. cit.*).

Experimental

Crotonyl chloride was prepared as before (*loc. cit.*).

Phenolic esters of crotonic acid were prepared in the usual manner as described in the earlier parts of this series. They are summarised in Table I.

Table I

Crotonate.	B. P.	Yield	Mol. formula.	% Carbon Found.	% Carbon Calc.	% Hydrogen. Found.	% Hydrogen. Calc.
Thymyl	138°/4 mm.	93.56%	$C_{14}H_{18}O_2$	76.82	77.05	8.02	8.26
Carvacryl	150°/5	91.72	$C_{14}H_{18}O_2$	76.68	77.05	8.13	8.26
p-Chlorophenyl	154°/9	88.88	$C_{10}H_9O_2Cl$	60.82	61.07	4.14	4.58
p-Bromophenyl	142°/5	92.06	$C_{10}H_9O_2Br$	49.62	49.80	3.44	3.73

Fries rearrangement of the ester was carried out for one hour at 120° (without solvent) as described in the earlier parts of this series. The *o*-hydroxyketones obtained are summarised in Table II.

TABLE II

o-Hydroxyketone.*	Ketone. B.P. or m.p.	Yield.	% Carbon. Found.	% Carbon. Calc.	% Hydrogen. Found.	% Hydrogen. Calc.	2:4-Dinitrophenylhydrazone. Mol. formula.	M.p.	% Nitrogen. Found.	% Nitrogen. Calc.
2′-Hydroxy-6′-methyl-3′-*iso*propylphenyl-β	175°/5 mm.	72.0	76.72	77.05	8.03	8.26	$C_{20}H_{22}O_5N_4$	162°	6.96	7.11
2′-Hydroxy-3′-methyl-6′-*iso*propylphenyl-β	168°/5	78.0	76.83	77.05	8.09	8 26	$C_{20}H_{22}O_5N_4$	203°	6.75	7.11
2′-Hydroxy-5′-chlorophenyl-β	112°	69.0	60.93	61.07	4.16	4.58	$C_{16}H_{13}O_5N_4Cl$	223°	14.51	14.87
2′-Hydroxy-5′-bromophenyl-β	107°-108°	70.0	49.54	49.80	3 68	3.73	$C_{16}H_{13}O_5N_4Br$	234°	12.85	13.30

*β denotes-butene-2-one-1

Effect of Temperature on Fries Rearrangement.—The reaction in all the cases was carried out for one hour at four different temperatures viz., 100°, 120°, 140° and 160° (without solvent) when 1 part of the ester was added to 1.5 parts of anhydrous aluminium chloride. After completion of the reaction the mixture was decomposed with ice and dilute hydrochloric acid and extracted with ether. The hydroxyketones were isolated as a yellow crystalline sodium salt by the addition of dilute caustic soda solution to the ether extract. The crystalline sodium salt was collected at the pump, washed with ether and decomposed with dilute hydrochloric acid when the hydroxyketone separated as an oil. It was then extracted with ether and dehydrated over anhydrous sodium sulphate. After removal of the solvent the hydroxyketones were distilled under reduced pressure. The results are summarised in Table III.

TABLE III

Ester.	Amt. taken.	Yield of *ortho*-hydroxyketones at 100°.	120°.	140°.	160°.
Thymyl acetate	5.0 g.	1.6 g.	4.2 g.	3.5 g.	* 3.0 g.
Carvacryl acetate	5.0	1.9	4.0	3.2	* 2.9
m-Ethylphenyl acetate	5.0	2.05	4.3	3.0	* 2.7
3:5-Dimethylphenyl acetate	5.0	1.8	4.05	3.15	* 2.8
Thymyl crotonate	5.0	1.65	3.6	* 2.5	* 2.1
Carvacryl crotonate	5.0	1.95	3.9	* 2.3	* 1.9

* With charring.

Effect of Solvent on Fries Rearrangement.—The reaction was carried out in the presence of 15 c.c. of dry and freshly distilled solvent with ester (1 part) and finely powdered anhydrous aluminium chloride (1.5 parts). The reaction in the case of carbon disulphide was first carried out in a boiling water-bath for half an hour and in an oil-bath at 120° for an additional half hour after removal of the solvent. The reaction was carried out at 60° for one hour in the case of nitrobenzene and at 100° for one hour in toluene and xylene. After completion of the reaction the mixture was decomposed with ice and dilute hydrochloric acid. Nitrobenzene was removed by steam distillation while toluene and xylene were removed by distillation under reduced pressure. The *ortho*-hydroxyketones were isolated from the residual oil in the usual way as described in the previous case. The results are summarised in Table IV.

TABLE IV

Ester.	Amt. taken.	Yield of *ortho*-hydroxyketone in CS_2.	Nitrobenzene.	Toluene.	Xylene.	Without solvent.
Thymyl acetate	5.0 g.	3.25 g.	3.40 g.	3.0 g.	2.95 g.	4.2 g.
Carvacryl acetate	5.0	3.15	3.35	2.9	3.06	4.0
m-Ethylphenyl acetate	5.0	3.10	3.25	2.8	2.85	4.3
3:5-Dimethylphenyl acetate	5.0	3.40	3.35	3.06	3.10	4.05
p-tert.-Butylphenyl crotonate	5.0	1.55	2.85	2.65	2.73	3.15
3-Methoxyphenyl crotonate	5.0	2.10	3.00	2.85	2.90	3.30

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SYNTHESIS OF 4: 4′-DIAMINODIPHENYLSULPHONE

By K. Raman, M. Raghavan and P. C. Guha

Barring one or two, the methods of synthesis of 4:4′-diaminodiphenylsulphone are very tedious, involving many complicated stages, giving poor yields. The method of synthesis, recorded in this paper, has two distinct advantages in that the method of preparation is easier and the yield, better than that in the previous methods.

4:4′-Diaminodiphenylsulphone (D. D. S.) and its derivatives are widely used in the treatment of lepromatous and tuberculoid leprosy. This sulphone has been synthesised by a number of methods (cf. Swiss Pat. 243601; *Chem. Abs.*, 1949, **43**, 7960, Hung. Pat. 120021; *Chem. Abs.*, 1939, **33**, 4600). According to a seemingly simple method (Swiss. Pat. 243601), *p*-acetaminobenzene sulphonyl chloride is added gradually to a mixture of acetanilide and anhydrous aluminium chloride at 160°, and the product worked up. We tried this method and were confronted with a number of difficulties while carrying out the process. A uniform molten mixture of the reactants was not obtained and the decomposition of the reactants set in during the course of the experiment.

In order to obviate the disadvantages mentioned above, the condensation of acetaminobenzene sulphonyl chloride with acetanilide in presence of aluminium chloride was carried out in an inert solvent such as nitrobenzene in which the reactants and the aluminium chloride were soluble.

The process consists in gradually adding small quantities of acetaminobenzene sulphonyl chloride to a solution of acetanilide or *vice versa* in nitrobenzene in the presence of aluminium chloride at a temperature of about 140°-145°. According to this method it is possible to operate with greater ease and to get good yields of *bis*-(4-acetaminophenyl)-sulphone which in turn can be hydrolysed to *bis*-(4-aminophenyl)-sulphone with dilute hydrochloric acid.

The influence of the concentration of the reactants and anhydrous aluminium chloride, the nature and quantity of the inert solvent, the temperature and duration of the reaction on the yield of *bis*-(4-acetaminophenyl)-sulphone was studied in detail. Nine experiments were conducted according to the above defined method of preparation with a view to standardising the conditions of the process.

A reaction carried out with carbon disulphide as a solvent did not yield any tangible result. Probably this is due to the low temperature attainable while working with this solvent.

It has been observed that good yields of sulphone are obtained if the reaction temperature is maintained at about 140°-145° in contrast to 160° of the previous method. This factor is of importance, for the decomposition temperature of *p*-acetaminobenzene sulphonyl chloride is 149°.

The condensation is best carried out with acetanilide, *p*-acetaminobenzene sulphonyl chloride and aluminium chloride in such molar proportions as 1:1:

The use of a high boiling inert solvent such as nitrobenzene and the control of the reaction temperature are essential factors for the success of the process.

Experiments were also conducted to find out whether the condensation between *p*-nitrobenzene sulphonyl chloride and acetanilide under similar conditions would proceed using carbon disulphide and nitrobenzene as solvents. The condensation did not proceed, evidently due to the inactivation of the aromatic nucleus by the nitro group of *p*-nitrobenzene sulphonyl chloride. *p*-Chloroacetanilide from the chlorination of acetanilide was isolated as a product.

The following account gives a detailed procedure for the preparation of D. D. S.

Acetanilide (3.4 g.) was added gradually to a solution of *p*-acetaminobenzene sulphonyl chloride (5.8 g.) (purified by crystallisation from an appropriate solvent like ethylene dichloride) and anhydrous aluminium chloride (12 g.) in dry nitrobenzene (20 c.c.) at 140°-145° under stirring. After completion of addition, the reaction was continued for about 2 hours. The cold reaction mixture was poured into water (50 c.c.), acidified with hydrochloric acid. The *bis*-(4-acetaminophenyl)-sulphone (5.3 g.) separated as a light chocolate coloured precipitate. It was filtered and washed several times with water and if nscessary, with a little of an organic solvent like ether. The nitrobenzene layer on being worked up was found to contain only traces of *bis*-(4-acetylaminophenyl)-sulphone.

bis-(4-Acetylaminophenyl)-sulphone was crystallised from dilute acetic acid, m. p. 283-85°. The free base was obtained by hydrolysis with dilute hydrochloric acid. The precipitate of D. D. S., obtained after neutralisation with ammonia, was recrystallised from dilute alcohol, m.p. 172-74°, yield 3.7 g.

The reaction outlined above was carried out with the variation of adding *p*-acetaminobenzene sulphonyl chloride to acetanilide in nitrobenzene solution. The results were very nearly identical with that of the above experiment.

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ON THE RELATIONSHIP BETWEEN VISCOSITY AND VAPOUR PRESSURE OF LIQUIDS

By Asoke Kumar Mukherjee

A relationship between fluidity and vapour pressure of liquids and temperature has been worked out on the assumption of free volume in liquids in which the liquid molecules undergo translational motion, and the equation verified in 20 liquids some of which have been shown in the paper.

It is often a matter of common experience that highly viscous liquids have lower vapour pressure, while the vapour pressures of readily mobile liquids are in general higher. Earlier attempts to connect viscosity and vapour pressure centred round such analogies or similarities in the behaviour of these two entities, but the cause of such parallelism was never traced, not even qualitatively. Thus, Porter (*Phil. Mag.*, 1912, *vi*, **23**, 458) first pointed out that the Ramsay-Young rule for the vapour pressure of two liquids was obeyed by their viscosities as well, and concluded that, since, according to this rule, the vapour pressure was connected with temperature by the relation

$$f(p) = a + b/T \qquad \ldots \quad (1)$$

viscosity would also be related to temperature by a similar equation

$$F(\eta) = A + B/T \qquad \ldots \quad (2)$$

where $f(p)$ and $F(\eta)$ represented certain functions of p and η respectively and a, b, A and B were constants. Comparing equation (1) with the integrated form of Clausius-Clapeyron equation

$$\ln p = j - L/RT \qquad \ldots \quad (3)$$

it is suggestive that b in equation (1) may be in some way related to L, the latent heat of vaporisation per mole of the liquid. Encouraged by this similarity of equations (1), (2) and (3), Dunn (*Trans. Faraday Soc.*, 1926, **22**, 401) called B in equation (2) the heat of cohesion, *i.e.*, the energy necessary for a molecule to overcome the attraction of its neighbours.

Later on the development of a viscosity-temperature relationship by Andrade (*Phil. Mag.*, 1934, **17**, 497, 698) in the form

$$\log (1/\eta) = A - B/T \qquad \ldots \quad (4)$$

opened up fresh possibilities for establishing a rational connection between these two entities along considerations fundamentally different from those pointed out by Porter (*loc. cit.*). Apart from the considerations of analogy (cf. Porter), Drucker (*Z. physikal. Chem.*, 1918, **92**, 287) from his experimental investigations first proposed an empirical relation between viscosity and vapour pressure as follows

$$\log (1/\eta) = \rho - \mu \log p \qquad \ldots \quad (5)$$

where ρ and μ are constants. Drucker was of opinion that divergence from this equation occurred specially in strongly associated liquids. Andrade (*loc. cit.*) pointed out that a relationship like that of Drucker could be arrived at as a corrolary to his viscosity-tem-

perature relationship by a straight-forward comparison with the integrated form of Clausius-Clapeyron equation.

But besides such attempts resting on similarities and analogies, no systematic attempt can be found in the literature to connect these entities rationally. The present communication reports an attempt in this direction.

Relationship between Viscosity and Vapour Pressure

In order to correlate these two important properties of liquids, the picture of the liquid state of aggregation, as presented by the author in a previous communication, has been invoked (Mukherjee, this *Journal*, 1949, **26**, 493). It has been mentioned that liquids possess free volume which increases with rise of temperature (*ibid.*, 1950, **27**, 599; 1951, **28**, 363) and thus increases the average distance between molecules in the liquid. This causes a decrease in the intermolecular attraction, or the internal pressure of the liquid, which has an effect in controlling the escaping tendency of a molecule; and since the escaping tendency increases as the internal pressure diminishes, the vapour pressure increases in consequence. Again, an increase in free volume (v_f) is expected to increase the fluidity (ϕ), the reciprocal of the coefficient of viscosity, in a linear manner (vide Mukherjee, *ibid.*, 1951, **28**, 365) from which it is easy to follow at least qualitatively as to how the fluidity of a liquid will increase with vapour pressure.

A quantitative relation can, however, be gathered from a previous communication of the author (*ibid.*, 1951, **28**, 519) where fluidity is related to the free energy of a liquid. It is, however, a common knowledge from thermodynamics that free energy and vapour pressure are related closely, so much so that they serve as measures of each other. From equation (7) of the above communcation,

$$\log \phi + 3/2 \log T = \alpha + \beta/T \quad \ldots (6)$$

it is evident that the quantity ($\log \phi + 3/2 \log T$) is a linear function of $1/T$. Again from Clausius-Clapeyron equation it is well known that $\log p$ is also a linear function of $1/T$ from which it is easy to follow that the two quantities ($\log \phi + 3/2 \log T$) and $\log p$ will also be linearly related. The relationship will be of the form

$$\log \phi + 3/2 \log T = a + b \log p \quad \ldots (7)$$

where a and b are constants. This proposed relationship suffers from the drawback that the nature of the constants a and b is not known.

Verification of the proposed Equation

This equation has, however, been tested in about 20 liquids some of which have been shown in Figs. 1 and 2 by plotting $\log \phi + 3/2 \log T$ against $\log p$ at the same temperature. The graph is expected to be a striaght line which has been amply verified.

In this connection a reference may be made to the review of Madge (*Physics*, 1934, **5**, 39) on the relationship between these two entities. He remarks that since vapour pressure and fluidity both follow Ramsay-Young rule and since the relationship between vapour pressure and temperature is more accurately represented by the equation

$$\log p = A - B/T + C \log T \quad \ldots (8)$$

FIG. 1

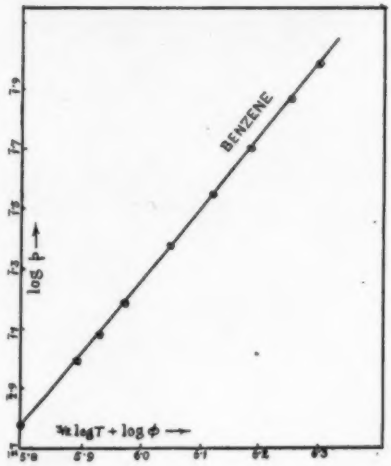
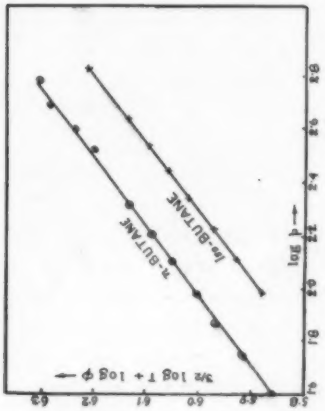


FIG 2



the fluidity will also be represented by

$$\log \phi = \gamma - \delta/T + \varepsilon \log T \qquad \ldots \quad (9)$$

Such a relationship has already been deduced in a previous communication (this *Journal*, 1951, **28**, 519). Eliminating $1/T$ from (8) and (9), it is possible to arrive at a relation like (7).

Thus, it is possible from considerations of free volume in liquids to understand a relationship between its viscosity and vapour pressure. The actual relationship, as presented in equation (7), contains a function of temperature also ($3/2 \log T$). Hence the variations of vapour pressure and fluidity will naturally be influenced by a variation of temperature.

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